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A.M.A. JOURNAL OF

DISEASES OF CHILDREN

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Mild Neonatal Toxoplasmosis
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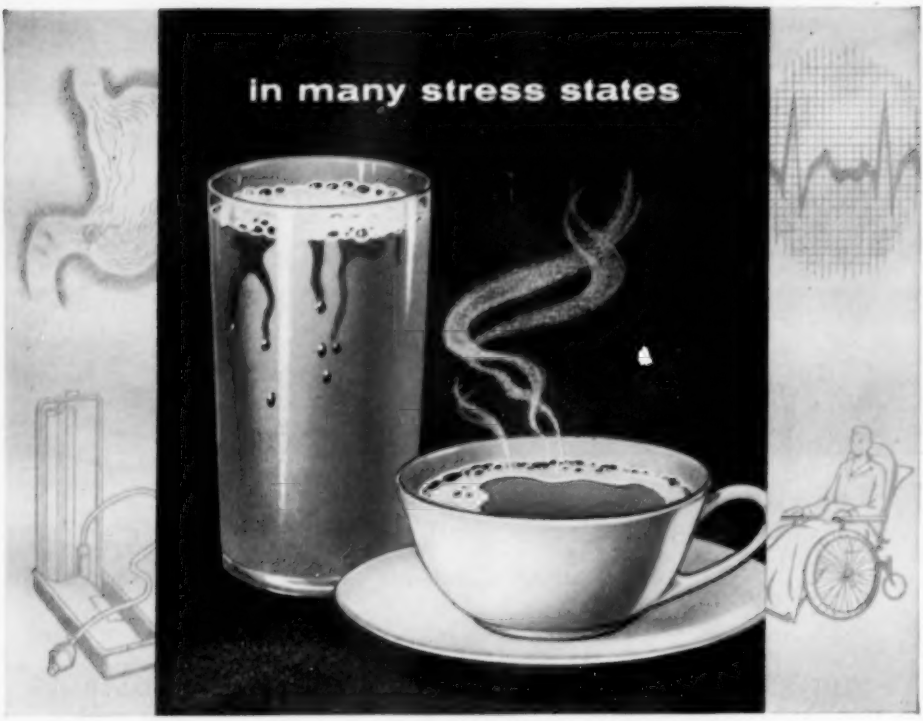

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1. Jackson, P. L.: Iron Deficiency Anemia in Infants, Editorial, J.A.M.A. *160*:976 (Mar. 17) 1956.

2. Martin, E. A.: Roberts' Nutrition Work with Children, Chicago, The University of Chicago Press, 1954, p. 211.

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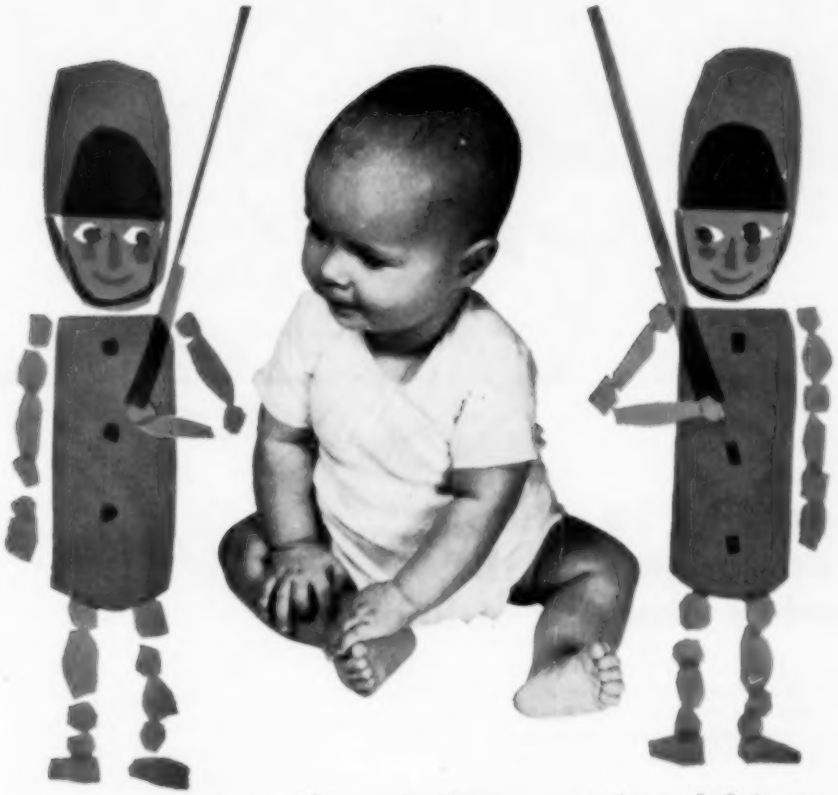

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(1) Diamond, L. K.; Smith, N. J., and Vaughan, V. C., III, in Nelson, W. E.: Textbook of Pediatrics, ed. 6, Philadelphia, W. B. Saunders Company, 1954, p. 962. (2) Niccum, W. L.; Jackson, R. L., and Stearns, G.: A.M.A. Am. J. Dis. Child. 86:553, 1953.

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DISEASES OF CHILDREN

Studies on Familial Nephrosis

I. Clinical and Pathologic Study of Four Cases in a Single Family

ROBERT L. VERNIER, M.D.; JOEL BRUNSON, M.D., and ROBERT A. GOOD, M.D., Minneapolis

The nephrotic syndrome has rarely been observed in more than one member of a family and is not generally considered to be a familial disease. Prader [1] and Goettsch,[2] however, reported the occurrence of the nephrotic syndrome in twins. Barnett [3] has observed nephrosis in two siblings of three families and Werner [4] in siblings of two additional families. Recently Fanconi [5,6] summarized the experience of his clinic with regard to the familial incidence of the nephrotic syndrome in 17 children of seven families. He concluded that nephrosis may occur as a familial disease and that the disease tends to be severer in older members of the family. He also stated that the prognosis of familial nephrosis seemed to be worse than that usually accorded the sporadic form of nephrosis.

This report presents the results of a study of a family in which all four children suffered from the nephrotic syndrome. Since we consider it likely that nephrosis occurring in several members of a family has a single etiology, we find it attractive to view our experience as an "experiment of nature" [7] providing an incisive opportunity to study the interrelationships of pathogenesis, clinical course, pathology, and genetic factors in this disease.

The purpose of this paper is to affirm the existence of familial nephrosis, to describe the clinical forms observed in the family we have studied, to present the spectrum of pathology as revealed by surgical biopsy of the kidney in these patients, and to attempt to draw some conclusions which we believe contribute to an understanding of the nephrotic syndrome as it occurs in the population at large.

Report of Case

CASE 1.—A boy was born Aug. 23, 1947 and died May 22, 1955. He was thought to be normal until 4 months of age, when swelling of his eyes and extremities was noted. Edema was present intermittently but was not investigated further until he was hospitalized at one year of age for treatment of a febrile illness associated with increasing edema. At that time he was found to have albuminuria, pyuria, and cylindruria which was interpreted as evidence of pyelonephritis. He was treated with antibiotics and his fever abated but the urinary abnormalities and the edema persisted.

He continued to have intermittent edema but otherwise was well until the age of 2½ years, when he was again hospitalized, for intussusception of the transverse colon which required surgical correction. In addition to the abdominal ab-

Submitted for publication Aug. 6, 1956; accepted Oct. 17.

Postdoctorate Fellow of the U. S. Public Health Service (Dr. Vernier).

American Legion Memorial Heart Research Professor of Pediatrics (Dr. Good).

From the Pediatric Research Laboratories of the Variety Club Heart Hospital and the Department of Pathology, University of Minnesota.

Aided by grants from the American Heart Association, U. S. Public Health Service, the Helen Hay Whitney Foundation, and the Graduate School of the University of Minnesota.

normalities he was found to have generalized edema and moderately severe hypertension (B. P. 130/90-150/100 mm. Hg). Laboratory studies revealed a blood urea nitrogen (BUN) of 14 mg. per 100 cc., serum albumin of 2.0 gm. per 100 cc., and serum globulin of 2.3 gm. per 100 cc. The serum cholesterol was 500 mg. per 100 cc. and the erythrocyte sedimentation rate (ESR Westergren) 110 mm. per hour. A routine urinalysis revealed 3+ albumin, occasional white blood cells, red blood cells, and hyaline casts.

Four subsequent hospitalizations were necessitated by intercurrent infections. At each admission the abnormalities of his serum chemistries and urinalysis persisted with slight variations. He continued to have intermittent edema and constant hypertension of moderate severity. Twice he was given serum albumin intravenously, which resulted in diuresis but did not alter significantly the clinical course of the disease.

He was first seen at the University of Minnesota Hospitals in 1953, at the age of 6 years. At this time he was edematous but did not otherwise appear ill. Funduscopic examination revealed slight narrowing of the retinal arterioles. A Grade 2 systolic heart murmur was heard at the apex. His blood pressure was 130/100 mm. Hg. He had ascites and pitting edema of the extremities. A right indirect inguinal hernia was present.

The significant laboratory findings at the time of this admission included the following: BUN 10 mg. per 100 cc., serum albumin 0.7 gm. per 100 cc., serum cholesterol 474 mg. per 100 cc., serum cholinesterase 1.36ΔpH units per hour, and ESR 115 mm. per hour. An Addis count revealed 3.0 gm. albumin; 1,367,000,000 RBC, and 537,000 casts in a 12-hour urine specimen. X-ray examination of the chest revealed questionable left ventricle enlargement. An intravenous pyelogram revealed normal excretion of the dye, but a double pelvis and double ureter were noted on the left. No attempt at specific treatment was made and he was followed in the outpatient department.

Fig. 1.—Photograph of Case 1 at age 6½ years. Note the marked edema and ascites.

Six additional admissions to the hospital were necessary during the next two years. Each admission was preceded by a marked increase in edema, ascites, and on several occasions pleural effusion. Figure 1 illustrates the degree of edema present at this time. Corticotropin (ACTH) treatment was begun, but the development of severe hypertension (160/100) forced its discontinuation. Five attempts to induce a remission by treatment with mechlorethamine hydrochloride (nitrogen mustard, HN_2, 0.4 mg. per kilogram i. v. in each two-day course) were unsuccessful. Two attempts to infect him with malaria (Plasmodium vivax) by the injection of 10 cc. of blood containing living organisms failed to produce clinical evidence of infection.

Attempts to reduce his blood pressure with reserpine and hydralazine were moderately successful. The maximal dose used was 2.0 mg. reserpine (Serpasil) and 200 mg. of hydralazine (Apresoline) hydrochloride per day. On this regimen for an interval of three months his blood pressure dropped to 135/85.

A surgical renal biopsy was done in February, 1955. The findings will be described below.

Following response to the antihypertensive therapy another course of corticotropin was given in April, 1955, in a dosage of 160 mg. per day intramuscularly (150 mg. per square meter of surface area). On the sixth day of therapy hypertension developed (B. P. 160/120 mm. Hg), and the corticotropin was gradually discontinued. Shortly after discontinuation of this therapy he developed azotemia, hyperkalemia, and acidosis. In spite of every effort to correct the chemical abnormalities, the renal insufficiency progressed and he died on May 22, 1955. An autopsy was done and a description of the findings will be presented below.

Case 2.—Born on Jan. 5, 1949, this child's development and general health were excellent until the age of 5½ years (October, 1954), when albuminuria (1+) and occasional granular casts were noted in a urinalysis obtained during a routine preschool examination. Five months earlier he had been examined by his local physician, and a urinalysis was reported to be negative. Because of the family history of nephrosis he was referred to the University of Minnesota Hospitals for study.

A physical examination was negative. The important laboratory studies at that time included the following: BUN 16 mg. per 100 cc., serum albumin 3.2 gm. per 100 cc., serum cholesterol 196 mg. per 100 cc. serum cholinesterase 1.20ΔpH units per hour, and ESR 85 mm. per hour. An Addis count revealed 0.5 gm. albumin, 1,000,000 RBC, and 20,000 casts in a 12-hour urine specimen. An intravenous pyelogram was normal.

He was followed in the outpatient department. Persistent albuminuria, cylindruria, and elevation of the ESR were noted until April, 1955. At that time his urine became free of albumin and his ESR declined to 12 mm. per hour. Serum chemistries in May and July, 1955, were as follows: blood urea nitrogen 14 mg. per 100 cc.; serum albumin 3.9 gm. per 100 cc.; serum globulin 3.0 gm. per 100 cc.; serum cholesterol 187 mg. per 100 cc. Repeat studies in February, 1956, eleven months after onset of the illness, were normal. Renal biopsy was done on May 4, 1956, and the findings will be described in the section on pathology below.

Case 3.—Born on Nov. 13, 1952, this girl was considered normal until 4 months of age, when she was hospitalized for treatment of bronchopneumonia. Persistent albuminuria and erythruria were noted at that time. She recovered rapidly from the illness but was hospitalized two weeks later, when she developed measles. Moderate albuminuria was again noted. Periorbital edema appeared at that time and has persisted throughout her illness. Over the subsequent 16 months she continued to be edematous and to show albumin, casts, and white cells on urinalysis. Because of the persistence of these findings and the onset of mild hypertension, she was referred to the University of Minnesota Hospitals at the age of 21 months. Figure 2 is a photograph of the patient at that time.

The significant physical findings included mild hypertension (B. P. 120/85 mm. Hg), minimal edema, questionable ascites, and slight hepatomegaly. The BUN was 10 mg. per 100 cc., the serum albumin 1.5 gm. per 100 cc., the serum cholesterol 415 mg. per 100 cc., the serum cholinesterase 1.5ΔpH units per hour, and the ESR 88 mm. per hour. An Addis count revealed 2.0 gm. albumin, 20,000,000 RBC, and 900,000 casts in a 12-hour specimen. During the course of this hospitalization frank ascites developed. She was treated with intramuscular corticotropin, 40 mg. (100 mg. per square meter) for 10 days. Her blood pressure had risen to 150/100 mm. Hg by the end of the course of therapy, but otherwise she tolerated the drug well. After discontinuation of therapy her blood pressure returned to pretreatment level. No significant clinical or laboratory response was obtained, and she was discharged and followed in the outpatient department.

She was admitted for the second time in January, 1955, for further treatment. The physical examination was unchanged. Her blood pressure was 125/90 mm. Hg. A clot test for the characteristic cells of lupus erythematosus was negative.

A surgical biopsy of the right kidney was obtained in February, 1955. The patient tolerated the procedure well. The microscopic findings are described in the section on pathology which follows.

Because of the persistent hypertension the patient was treated with oral hydralazine hydrochloride, 40 mg. daily, and reserpine, 0.5 mg. daily, beginning Feb. 26, 1955. The dose of hydralazine hydrochloride was gradually increased to levels of 80 mg. daily by March, 1955, at which time her blood pressure had fallen to 100/70 mm. Hg.

At that time corticotropin was given in a dose of 100 mg. (150 mg. per square meter) i. m. daily for a total of 17 days, but no laboratory or clinical evidence of improvement was noted.

In July, 1955, the patient was readmitted because of a severe respiratory infection. There had been a further decrease in the serum proteins, and the serum albumin was 0.3 gm. per 100 cc. She was given mechlorethamine hydrochloride intravenously in a dose of 0.2 mg. per kilogram of body weight on two consecutive days, but no clinical or laboratory evidence of improvement was noted. A second similar course of mechlorethamine hydrochloride, combined with daily intravenous infusion of salt-free serum albumin, was likewise ineffective.

She was readmitted for a fourth time, in January, 1956. Physical examination again revealed mild hypertension (B. P. 124/80 mm. Hg), pretibial edema, and ascites.

The laboratory findings of significance included the following: 4+ albuminuria, 1+ erythruria, and 2+ fine granular casts; BUN 10 mg. per 100

Fig. 2.—Photograph of Case 3 at age 2½ years. Note the generalized edema and ascites.

cc.; total protein 3.8 gm. per 100 cc.; serum albumin 0.5 gm. per 100 cc.; serum globulin 3.3 gm. per 100 cc.; serum cholesterol 628 mg. per 100 cc.; ESR 122 mm. per hour; serum electrolytes normal. A 12-hour urine specimen contained 97,000,000 red blood cells, 1,207,000,000 white blood cells, 139,000 casts, and 2.5 gm. of protein.

An injection of 10 cc. of blood containing living Plasmodium ovale malariae parasites was given, but no fever or clinical malaria resulted and there was no change in the patient's clinical or laboratory findings.

CASE 4.—This girl was born Jan. 6, 1955. The presence of the nephrotic syndrome in three children in this family prompted us to make arrangements for the delivery of this the fourth child at the University of Minnesota Hospitals. A 3640 gm. girl was born after a normal labor and delivery. A striking amount of thick, yellow vernix covered the infant, but the physical examination was otherwise not remarkable.

Studies of the cord blood revealed a serum albumin of 3.1 gm. per 100 cc., serum globulin 2.6 gm. per 100 cc., serum cholesterol 120 mg. per 100 cc., serum cholinesterase 0.52ΔPh units per hour. The first urine voided contained 2+ albumin and occasional white and red blood cells.

The child had a normal postnatal course and was discharged. At one month of age definite periorbital edema was noted by the child's mother. A urinalysis at that time revealed 4+ albuminuria and occasional red and white blood cells and fine granular casts.

At 2 months of age the child was admitted to the hospital for further study. The physical examination revealed pallor of the skin, periorbital edema, and minimal pitting edema of the lower extremities. Her weight was 5400 gm. Her blood pressure was 85/65 mm. Hg. The laboratory studies obtained at this admission included a BUN of 13 mg. per 100 cc., serum albumin 2.2 gm. per 100 cc., serum cholesterol 215 mg. per 100 cc., serum cholinesterase 1.5ΔpH units per hour, and ESR 85 mm. per hour. An Addis count revealed 0.9 gm. albumin, 37,000,000 RBC, and 26,000 casts in a 12-hour specimen. Although x-rays of the chest were interpreted as suggesting congenital heart disease, subsequent detailed study ruled out this possibility.

On April 18, 1955, a surgical biopsy of the right kidney was performed. The infant's postoperative course was uneventful. The microscopic findings are described below in the section on pathology.

She continued to have slight edema of the extremities. On May 25, 1955, corticotropin was administered in a dose of 50 mg. (150 mg. per square meter per day) intramuscularly for 12 days. Moderate hypertension developed near the end of the therapy, but her blood pressure returned to pretreatment levels after corticotropin was discontinued. There was no change in the patient's weight or urinary and chemical abnormalities.

She was followed in the outpatient department. Repeated urinalyses revealed 2+ albumin and occasional WBC and RBC, and her sedimentation rate remained elevated (over 100 mm. per hour). There was a progressive decrease in the serum albumin level.

She was admitted to the hospital a third time, at one year of age. The physical examination again revealed moderate periorbital and pretibial edema and questionable ascites. No heart murmur of significance could be heard. Her blood pressure was 100/70 mm. Hg (sleeping).

Albuminuria (2 to 3+), hypoalbuminemia (1.1 gm. per 100 cc.), slight elevation of the serum cholesterol (281 mg. per 100 cc.), and elevation of the ESR (103 mm. per hour) were again noted.

Cortisone was given in a dose of 150 mg. (300 mg. per square meters per day) for 15 days, then gradually decreased over the next five days. Again her blood pressure rose to levels of 150/100 by the 14th day of therapy. After discontinuation of the hormone there was no diuresis and no changes in her clinical picture or laboratory features occured.

Table 1 summarizes the maximal clinical and laboratory abnormalities manifested by these patients during the period of observation. It is apparent from the case reports just presented that the characteristic abnormalities of the nephrotic syndrome—edema, albuminuria, hypoalbuminemia, hypercholesterolemia, and elevation of the erythrocyte sedimentation rate—were all present in three of the children during the course of their illness. The fourth child, Case 2, was found to have albuminuria and elevation of the ESR without pronounced alteration of the serum albumin fraction, or serum cholesterol levels, and without edema. Although as an isolated case one might question the diagnosis of nephrosis in this patient, it seems reasonable, in light of the family history, to conclude that the development of a persistent albuminuria and an elevated sedimentation rate in this patient reflects the occurrence of a mild episode of the nephrotic syndrome at a subclinical level.

TABLE 1.—*Summary of Clinical and Laboratory Manifestations of Familial Nephrosis*

Case, Age (Yr.), Sex	Edema	Ascites	Hypertension	Frequent Infections	Addis Count			Serum Albumin, Gm/100 Cc.	BUN, Mg/100 Cc.	Cholesterol, Mg/100 Cc.	ESR, Mm/Hr.	Cholinesterase, ΔpH U/Hr.
					Alb., Gm.	RBC, Million	Casts, Thous.					
Case 1 (6) M	++++	++++	+++	+++	3.0	1,307	537	0.7	10	500	115	1.36
Case 2 (6) M	....	....	....	....	0.5	1	20	3.2	16	196	85	1.20
Case 3 (2) F.	+++	++++	++	++	2.5	20	900	0.5	10	677	131	1.74
Case 4 (1) F.	++	++	....	....	0.9	37	26	0.8	13	281	116	1.70
Normal					0.04	<1	<10	3.6-5.6	<20	150-250	<20	0.52-1.08

TABLE 2.—*Renal Function in Familial Nephrosis*

Case	Age at Test	Wt., Kg.	Surface Area, Sq. M	C_{Urea}, Cc/Min.			C_{Inulin}, Cc/Min.			$C_{Creatinine}$, Cc/Min.			C_{PAH}, Cc/Min.			F.F.
				Obs	per 1.73 M²	% N	Obs	per 1.73 M²	% N	Obs	per 1.73 M²	% N	Obs	per 1.73 M²	% N	
	5½	25	0.85	66	134	191										
	6	29	0.95	38	69	100										
	7	30	0.97				48	71	59				229	408	68	0.20
	7½	31	0.98	16	28.2	40										
2	6	20	0.75				58.5	134	112				283	651	100	0.20
	7	26	0.88							55	108	90				
	1 9/12	13.6	0.57				50.2	152	127				187	568	90.4	0.27
3	2 5/12	15.4	0.61	55	156	220										
	2 10/12	17.0	0.65				82	218	181				311	825	137	0.24
	3 4/12	18.0	0.70							55	136	113				
4	3/12	5.6	0.30				12	70	58.3				88	500	80.3	0.14
	1	10.5	0.47							16.5	61	50.9				
Normal Adult		70	1.73		70			120			120			600		0.20

C = renal clearance.
Obs = observed value.
per 1.73 M² = corrected value related to adult surface area.
% N = per cent of normal value.
PAH = para-amino hippurate.
F.F. = filtration fraction.

Special Studies

An investigation of the renal physiology and pathology, adrenal function, protein metabolism, and immune response of the children reported in this study was undertaken to evaluate the significance of these factors in differentiating familial nephrosis from the sporadic disease.

Renal Function

Standard methods for the measurement of glomerular filtration rate (GFR) by inulin clearance (C_I), effective renal plasma flow (clearance of para-amino hippurate, PAH) and maximal tubular resorption of PAH (TM_{PAH}) were utilized. The mean value of three or more 15-minute study periods was recorded as the observed clearance value and corrections made for relative surface area in order to relate the results obtained to adult standards.

Table 2 lists the results of serial renal function tests of these children as determined by a variety of clearance methods.

A progressive decrease in the clearance of urea and inulin was observed in Case 1 over the 2-year period of observation preceding his death from renal insufficiency at 7½ years of age. The PAH clearance was proportionately reduced and the filtration fraction ($C_I/_{PAH}$) was consequently normal.

The clearance of inulin and PAH were normal in Case 2 during an episode of mild nephrosis. Ten months later, following apparent recovery from the disease, a creatinine clearance was also normal.

Moderately to markedly elevated clearances of urea, inulin, and PAH were observed in Case 3 during the first one and one-half years of the study. This was not surprising, since supernormal renal clearances have frequently been reported in children with nephrosis.[8]

Because of presumed immaturity of renal function, clearances of inulin and PAH are known to be reduced in infants as compared with adults, even when corrections are made for surface area. Thus, the value obtained for inulin clearance in Case 4 at 3 months of age is probably within the normal range or only slightly reduced when compared with that in normal infants of that age.[9] However, the clearance of creatinine observed when Case 4 was one year of age is lower than the expected normal for that age and may reflect increasing renal damage in this child.

The renal function studies in these children appear to follow the pattern of physiologic and pathologic variation expected of children with nephrosis. Metcoff et al.[10] reported the results of serial renal function tests in nephrotic children in which all the variations reported above were observed. A rough correlation was noted between the duration of the disease and progressive decrease in renal function as measured by the clearance of inulin and PAH. These authors concluded that a progressive pathologic alteration in renal hemodynamics was the natural consequence of chronic active nephrosis. Although the short duration of observation of the children in this study would make it unwise to predict the course of the pathologic physiology at this time, it seems likely that renal insufficiency will develop in Cases 3 and 4 unless a remission of the disease process occurs or can be induced by treatment.

[A subsequent second renal biopsy in Case 3 has confirmed this finding, in that moderately severe chronic glomerulonephritis has developed.]

Adrenal Function

The corticotropin-eosinophil response tests were conducted as outlined by Randolf.[11] Standard corticotropin-17-hydroxycorticosteroid (17-OHCS) response tests were performed as described by Ely et al.[12] The serum 17-OHCS and total corticosteroid levels were determined in the laboratories of the department of pediatrics of the University of Utah.*

There is increasing evidence that abnormal adrenal function may be present in patients with the nephrotic syndrome. McCall and Singer[13] and Farnsworth[14] have reported a subnormal excretion of urinary corticoids in nephrotic children who failed to respond to treatment with corticotropin, as compared with the excretion noted in child-

*Dr. Vincent Kelley performed these determinations.

ren who were benefited by this treatment. The significance of this observation has not been established.

Leutscher [15] reported that aldosterone was present in concentrations higher than normal in the urine of nephrotic patients. Although the role of this hormone in the pathogenesis of nephrosis is not clear at this time, it is conceivable that some alteration in adrenal physiology may be involved in the pathogenesis of nephrosis.

The adrenal function of the children presented in this study was evaluated by determination of (1) eosinophil response to a standard dose (25 mg.) of corticotropin and to surgical stress (renal biopsy); (2) urinary excretion of 17-ketosteroid and 17-hydroxysteroids, and (3) serum 17-hydroxycorticosteroids and total serum corticoid response to a standard injection of corticotropin (25 mg). The results of these studies are listed on Table 3. It is evident that a significant and normal decrease in total circulating eosinophils occurred in each case two hours after the injection of 25 mg. of corticotropin. The urinary 17-hydroxycorticosteroid and 17-ketosteroid excretion in a 24-hour specimen was normal. The fasting serum 17-hydroxycorticosteroid levels in these children were within normal range, although the response (2 hours) to 25 mg. of corticotropin was slightly less than the mean value for normal children.[12] It is of interest that similar subnormal responses to the standard serum 17-hydroxycorticoid-corticotropin test have been observed in other nephrotic children studied in our laboratory.[16] The significance of this evidence for slightly reduced adrenal function in nephrosis is not known.

TABLE 3.—*Adrenal Function*

Case	Total Eosinophils per Cc.						Urinary Corticoids Mg. per 24 Hr.		Serum Corticoids Response to 25 Mg. Corticotropin I. M.					
	Corticotropin Test, 25 Mg. I.M.			Surgical Biopsy					Control			2 Hr. Later		
	Control	2 Hr.	4 Hr.	Control	2 Hr.	4 Hr.	6 Hr.	17-OHCS	17-Keto CS	17-OHCS	Total CS	17-OHCS	Total CS
1	237	14		130	2		0	0.6	2.7	10.2			
2	144	6						3.0	6.4	11.6	98.7	19.4	112.8
3	313	41		98	3	0		0.6	4.7	14.5	166.0	28.7	414.0
4	222		37	87	19		28	1.4	0.9	14.7		19.4	

17-OHCS = 17-hydroxycorticosteroids.
17-Keto CS = 17-ketocorticosteroids.
Total CS = total corticosteroids.

Serum Protein Studies

Electrophoretic patterns were determined by paper electrophoresis, using a Spinco Apparatus, Model R, Series B, with a Durrum-type cell, and by free electrophoresis, using a Klett electrophoresis apparatus. Serum mucoprotein methods have been described previously.[17]

TABLE 4.—*Electrophoretic Protein Analysis—Familial Nephrosis*

Patient	Albumin	Globulins				Total Protein
		Alpha$_1$	Alpha$_2$	Beta	Gamma	
Case 1	0.9	0.2	0.6	1.8	0.1	3.6
Case 2	3.88	0.27	0.73	0.91	0.91	6.7
Case 3	0.7	0.05	2.1	0.75	0.19	3.8
Case 4	1.47	0.44	1.40	1.01	0.08	4.4
Normal	3.9±0.5*	0.2±0.1	0.6±0.1	0.9±0.2	1.1±0.3	

* ± Standard Deviation.

Electrophoresis of the serum of patients with nephrosis reveals a pattern characterized by a markedly decreased concentration of albumin and gamma-globulin fractions and relative or absolute increase in the concentrations of the alpha- and beta-globulins.[18] Typical fractional serum protein values obtained by electrophoresis of serum from the children reported in this study are listed in Table 4. Serial electrophoretic patterns varied only slightly from these values and failed to add any new information. The abnormalities of serum protein in our cases are similar to the values reported in other patients with nephrosis.

Kelley et al.[19] have shown that the serum mucoprotein level is characteristically very low in patients with lipoid nephrosis. Although occasional normal or high values for serum mucoprotein were observed, the mean level was only 68% of that observed in normal children. The occasional high values noted in nephrosis were present either early in the course of the disease or during partial remission. It was concluded by the authors that loss of mucoprotein in the urine during the active stages of the nephrotic syndrome probably accounted for the characteristic low values observed.

Determination of the serum mucoprotein and C-reactive protein levels in the children reported in this study (Table 5) revealed significantly low values in all of these patients except Case 2. The elevated mucoprotein level observed in this child early in the course of his disease is correlated with the minimal proteinuria noted at that time and appears to agree with reported results in other nephrotic children.[19]

TABLE 5.—*Mucoprotein and C-Reactive Protein Values*

Case	Mucoprotein, Mg/100 Cc.	C-Protein (0-4 +)
1	1.7	0
2	9.7	1+
3	1.54	0
4	2.2	0
Normal	2.49±0.06	0

Antistreptolysin O Titers

Antistreptolysin O (ASO) titers are characteristically low in the active phase of nephrosis.[20,21] Earle et al.[22] observed that the low level of ASO in active nephrosis failed to increase even in the presence of persistent infection with Group A hemolytic streptococci but that elevation of the ASO titer later occurred with the onset of renal insufficiency and loss of edema. Rytand does not believe that urinary loss of antibody accounts for the consistently low ASO titers observed in these patients.[21] Serial evaluation of ASO titers in the children reported in this study were observed to be very low throughout the active period of the disease (Table 6).

TABLE 6.—*Antistreptolysin Titers—Familial Nephrosis*

Patient	ASO Titer Todd U/Cc.
Case 1	<50
Case 2	<50
Case 3	<50
Case 4	<50
Normal	50–125 U/cc.

Family History

The occurrence of four cases of nephrosis in a single family prompted an investigation of the parents and a half brother of the children.

The frequent incidence of allergic manifestations in nephrotic children and in the families of children with nephrosis has been emphasized by Fanconi.[5] It is of interest that in the family reported in this

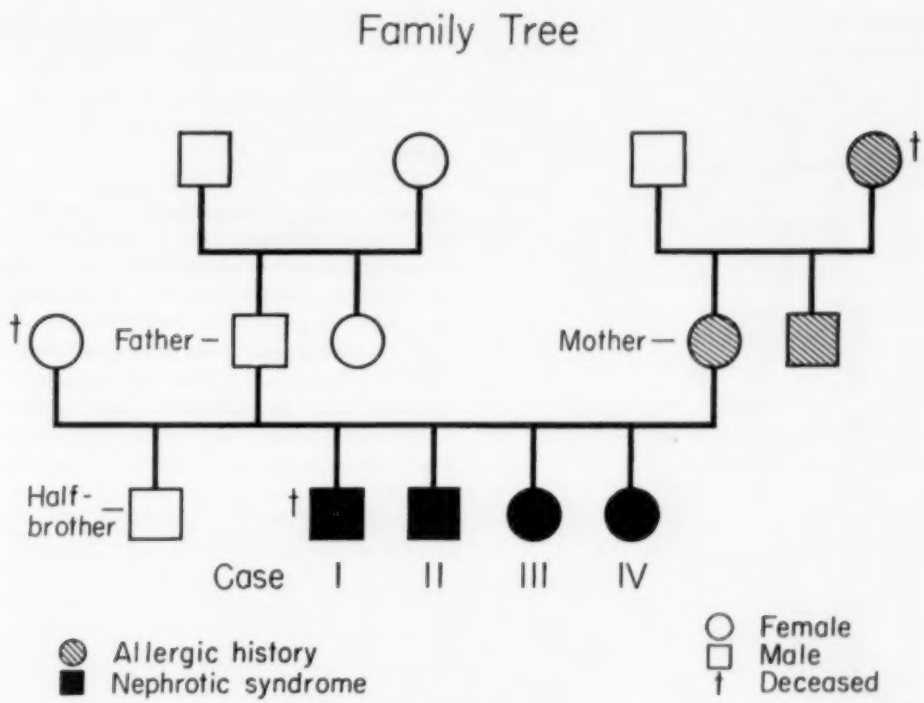

Figure 3.

study the maternal grandmother had severe asthma and hay fever; the children's mother and uncle had severe recurrent urticaria; Case 1 had eczema, and Case 3 has allergic bronchitis. There is no history of allergic disease in the paternal relatives or in the half brother (Fig. 3, Family Tree).

The children's mother was studied before and after the delivery of her fourth child (Case 4), in January, 1955. Her past medical history is of interest in that she had scarlet fever at 11 years of age, a "bladder infection" (details unknown) at 16 years of age, a "kidney infection" at 17 years of age, and gonorrhea at 18 years of age. Each of her four pregnancies was associated with the occurrence of mild to moderate hypertension, edema, and albuminuria during the last trimester.

One week prior to the delivery of her fourth child she was admitted to the obstetrical service of the University of Minnesota Hospitals because of complaints of headache, dyspnea, and increasing swelling of her legs. The significant physical findings included hypertension (B. P. 150/110) and 2+ edema of the lower extremities. The significant laboratory findings are listed in Table 7.

Treatment resulted in decrease of edema and fall in her blood pressure to 130/100 mm. Hg. The labor and delivery of Case 4 were uneventful. The mother's albuminuria disappeared shortly after parturition, and subsequent urinalyses have been normal.

The father of the children had never been seriously ill and no history of allergy or renal disease could be obtained. The results of his laboratory examinations are listed on Table 7.

A 17-year-old half brother of the children had never been seriously ill and had no history of allergic or renal disease. A summary of his laboratory findings is included in Table 7.

The significance of the poorly defined renal disease which the mother had in her youth and the preeclampsia which she had with each pregnancy is not known. Allen [23] regards preeclampsia as a type of membranous glomerulonephritis in which the pathologic lesion is indistinguishable from the renal lesion of nephrosis. He suggests that pregnancy may in some way activate an underlying pathologic renal process which is expressed clinically as preeclampsia with each pregnancy. Although the renal function

studies of the mother revealed a normal clearance of inulin and PAH and a normal TM_{PAH}, the marked decrease in phenolsulfonphthalein excretion observed on two occasions may reflect a residual renal lesion of significance.

The early onset and familial nature of the nephrosis suggested that a factor might exist in the maternal serum which, when transferred across the placenta, could result in injury to the fetal kidney. If an immune mechanism is responsible for nephrosis, as has been suggested by experimental studies,[24] it is conceivable that an antikidney antibody could be formed in the mother which would produce familial and congenital renal disease in her offspring after placental transfer by a mechanism similar to that resulting in erythroblastosis fetalis and congenital thrombocytopenic purpura. The origin of the nephrotoxic factor in the mother might be related to her previous kidney disease or might result from autoimmunization against some product of placenta.[25,26]

The possibility that such a circulating antikidney antibody in the serum of the mother might account for renal injury of her children was investigated by a search for antibody using the fluorescent tagging technique of Coons.[27]† Thus far no antibodies specific for glomeruli have been detected in the maternal serum, but further studies of this possibility are in progress.

TABLE 7.—*Summary of Laboratory Data—Parents and Half Brother of the Children*

Patient	Serum Proteins-Electrophoresis					BUN, Mg./100 Cc.	Cholesterol, Mg./100 Cc.	ESR, Mm./Hr.	Mucoprot., Mg./100 Cc.	ASO Units	C_{inulin}		C_{PAH}		Tm_{PAH}		Phenolsulfonphthalein	
	Alb.	Globulins									OBS	% N	OBS	% N	OBS	% N	15 Min., %	2 Hr., %
		Alpha 1	Alpha 2	Beta	Gamma													
Mother	2.8	0.2	1.0	0.9	0.8	8	232	38	3.7	100	164	100	732	100	98	100	12.5	50
Father	3.8	0.2	1.0	0.9	0.8	12	214	8	2.6	<50	90*	100					6.0	32
Half brother	4.3	0.3	0.9	0.9	1.3	12	192	1	2.5	<50	97*	100						

* Single injection technique.
C = renal clearance.
Obs = Observed value.
Tm PAH = maximal tubular excretion of para-amino hippurate.
% N = per cent of normal value.
PAH = para-amino hippurate.

Kidney Biopsy

The specimens from Cases 1, 2, and 4 were obtained by surgical exploration of the kidney under general anesthesia. The specimen from Case 2 was obtained by needle biopsy using the technique described by Meurecke et al.[28]

The tissue was fixed in 10% neutral formalin and processed in the usual manner. Paraffin sections were cut at 5μ, and these sections were stained with hematoxylin and eosin, azocarmine, and by the periodic acid-Schiff method. At least five sections of each

† Dr. Albert Coons, of the Harvard Medical School, is conducting this experiment.

biopsy were examined, taken from different portions of the paraffin block.

Summary of Pathologic Changes

The pathologic changes in the four cases presented may be summarized as follows:

CASE 1.—*Surgical Biopsy.*—Microscopically the capsular surface of the kidney was irregular and showed small depressions associated with tubular atrophy and interstitial fibrosis. The renal vessels appeared normal. Almost all the glomeruli appeared profoundly altered. Approximately 75% in any one field were shrunken and hyalinized, with complete obliteration of capillary loops. Occasional epithelial crescents were observed scattered through the section. The remaining glomeruli were large, bloodless, and distinctly lobulated, and there were varying degrees of coalescence and obliteration of the capillary loops, with capsular adhesions. Considerable quantities of Schiff-positive material were observed in these glomeruli. In an occasional glomerulus there were acute changes manifested by a marked increase in the number of endothelial nuclei, thickening of the capillary basement membranes, and numerous Schiff-positive hyaline thrombi in the capillary lumens.

The tubules showed pronounced atrophy, and there was considerable interstitial fibrous tissue proliferation and localized accumula-

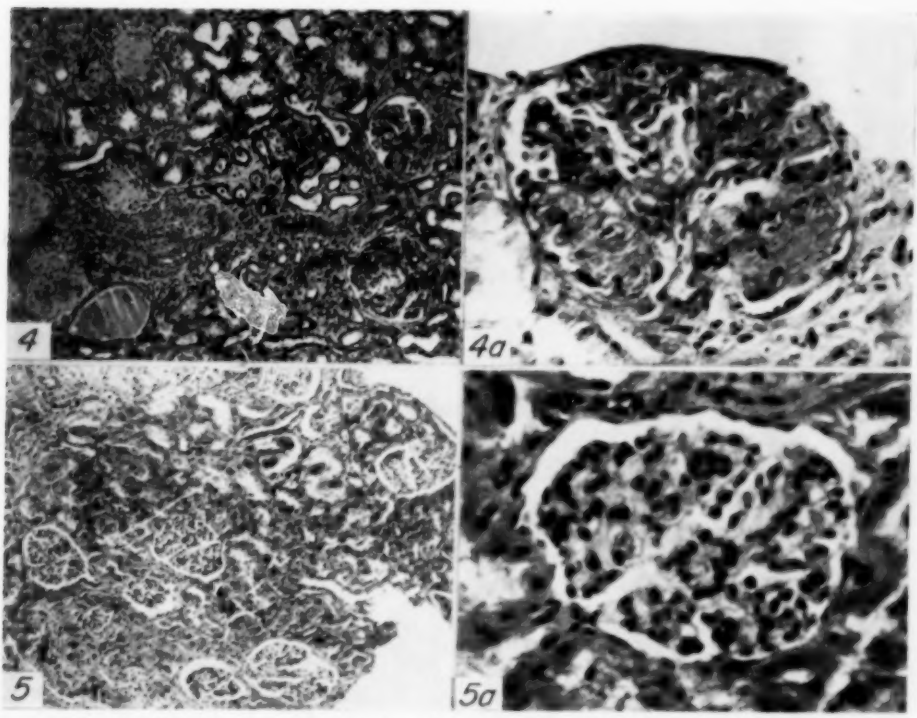

Fig. 4 (Case 1).—Low magnification of a section from the kidney showing four completely hyalinized, shrunken glomeruli on the left and two lobulated, enlarged glomeruli on the right. There is marked tubular atrophy and fibrosis and the remaining tubules appear hyperplastic; × 100.

Fig. 4A.—Higher magnification of a glomerulus from the same case as Figure 1, showing the distinct lobulation and coalescence and obliteration of capillary loops; × 450.

Fig. 5 (Case 2).—Low magnification section from needle biopsy of kidney, showing numerous normal glomeruli and tubules; × 100.

Fig. 5A.—Higher magnification of a glomerulus from the preceding section. The capillary loops appear open, and there is no evident increase in endothelial or epithelial cells; × 450.

tions of lymphocytes. Other tubules appeared markedly dilated and hyperplastic. Numerous deeply acidophilic casts were present in the tubular lumens (Figs. 4 and 4A). These changes were compatible with an active, chronic glomerulonephritis.

Autopsy (May 7, 1955): The significant gross findings included cardiac enlargement (200 gm.), pulmonary edema and bronchopneumonia, and an acute duodenal ulceration. The kidneys weighed 120 gm., and their capsules stripped with difficulty. The capsular surfaces were finely granular, and there was a small scar in the left kidney which represented the previous biopsy site. The cortices of the kidneys measured 4 mm. in thickness. Postmortem blood culture was sterile.

Microscopic examination confirmed the presence of pulmonary edema, pneumonia, and duodenal ulceration. Multiple sections from both kidneys showed diffuse involvement of the glomeruli, with varying degrees of hyalinization. Occasional large, bloodless, hypercellular glomeruli were noted, and there was pronounced tubular atrophy and interstitial fibrosis. The changes were similar to those observed in the biopsy specimen but were somewhat more pronounced. The final pathological diagnosis of the renal lesion was chronic active glomerulonephritis.

CASE 2.—*Needle Biopsy.*—Three fragments of renal tissue were examined. A

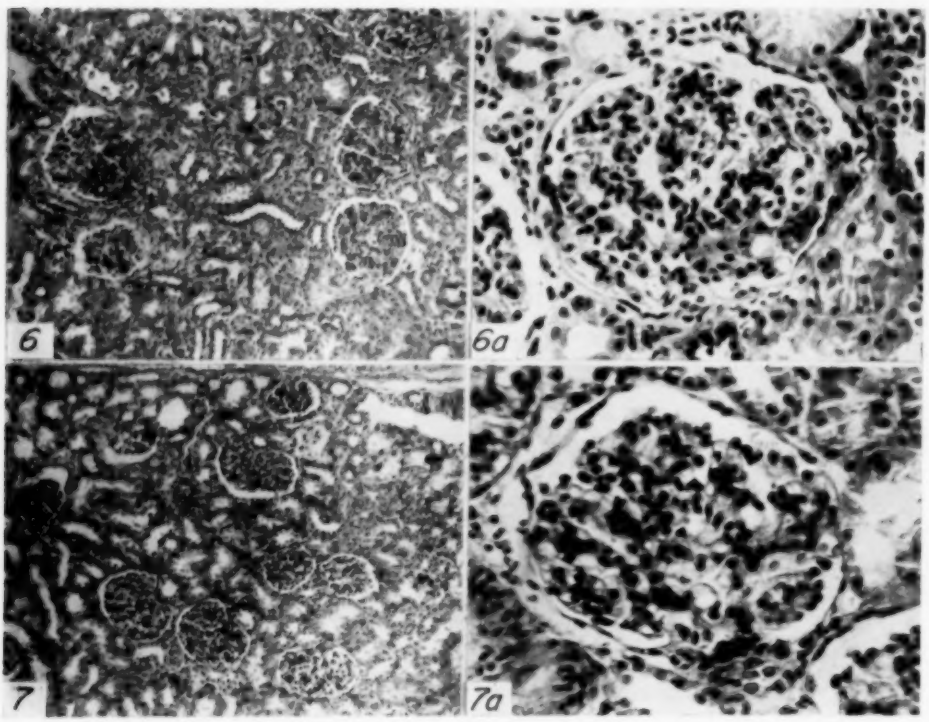

Fig. 6 (Case 3).—Low magnification of the kidney, showing uniform, diffuse glomerular involvement manifested by enlargement and hypercellularity. The tubules appear normal; × 100.

Fig. 6A.—Higher magnification of a glomerulus from the same section as Figure 2, showing the enlargement and increased number of endothelial cells. There also appears to be early epithelial-cell proliferation and glomerular tuft adhesion on the right; × 450.

Fig. 7 (Case 4).—Low magnification of a section from the kidney, showing normal glomeruli and tubules; × 100.

Fig. 7A.—Higher magnification of a glomerulus from the same section as the preceding figure, showing the open capillary loops and normal number of endothelial nuclei; × 450.

total of 13 glomeruli were present in the sections. In an occasional glomerulus there was a suggestive increase in endothelial nuclei, but the changes were not diagnostic. The glomeruli appeared to be of normal size, and there was no capillary basement membrane thickening. No changes were noted in the tubules or renal vessels. From this specimen, it was concluded that the kidney was histologically normal. The microscopic characteristics of this kidney are illustrated in Figures 5 and 5A.

CASE 3.—*Surgical Biopsy.*—Microscopic examination showed the capsular surface to be regular, and the renal vessels and tubules appeared normal. The glomeruli appeared distinctly enlarged and showed a definite, pronounced increase in number of endothelial nuclei. Few erythrocytes were noted in the capillary lumens. An occasional glomerulus was hyalinized, and there were scattered glomeruli which showed epithelial proliferation and early crescent formation. The capillary basement membranes did not appear thickened (Figs. 6 and 6A). These changes were consistent with the late stage of acute, or early stage of subacute, glomerulonephritis.

CASE 4.—*Surgical Biopsy.*—Histologic examination showed a smooth capsular surface and normal tubules and renal vessels. The glomeruli were of normal size, and there did not appear to be any definite increase in the number of endothelial or epithelial cells. The capillaries contained numerous erythrocytes, and special stains failed to reveal any basement membrane thickening (Figs. 7 and 7A). Microscopically, this appeared to be a normal kidney.

Relation of the Pathologic Changes to the Duration of the Disease Process

It seems noteworthy that a correlation exists between the duration of active nephrosis in each of the children in the family and the degree of pathologic alteration observed in the renal biopsy specimen (Table 8). This relationship would appear to support the concept of progressive renal damage in active nephrosis as suggested by the physiologic studies of Metcoff et al.[10]

Results of Therapeutic Attempts in Familial Nephrosis

Despite vigorous treatment, utilizing a variety of methods, representing virtually every form of therapy known to be effective in producing improvement in nephrosis, not a single significant remission has been observed in these children (Table 9). The resistance of familial nephrosis to treatment noted by Fanconi [5] is thus confirmed by the present study.

Comment

Data have been presented to document the occurrence of nephrosis in four children of a single family. The familial syndrome has been investigated in an attempt to detect differences in the clinical course, the pathologic physiology, and the pathology of the disease which might distinguish familial nephrosis from nephrosis as it usually occurs. It is apparent that nephrosis began at an early age in the members of this family. Familial nephrosis appears to be very resistant to all the forms of therapy which are known to produce remission in a large percentage of nephrotic children. These two factors confirm the similar findings reported by Fanconi [5] in a large series of familial cases of nephrosis.

In two of the children (Cases 1 and 3) edema was observed as early as 4 months of age, and protein was present in the urine of another child (Case 4) at birth. Rennie [29] has shown that proteinuria usually precedes the onset of edema by weeks or months. These observations suggest that the nephrotic syndrome observed in three of the children of this family was congenital as well as familial. Case 2, in whom proteinuria was not present at age 5 years but in whom proteinuria subsequently developed, apparently did not have congenital nephrosis.

The occurrence within the members of a single family of a clinical spectrum ranging from transient nephrosis, through persistent

TABLE 8.—*Relation of Pathology to Duration of Active Nephrosis*

Case	Age at Biopsy	Duration of Disease	Microscopic Diagnosis
2	7 yr.	1 yr. post-recovery	Normal
4	3 ½ mo.	3 ½ mo.	Normal
3	27 mo.	23 mo.	Subacute glomerulonephritis
1	7 yr.	6 ½ yr.	Chronic glomerulonephritis

pure nephrosis, to mixed nephrosis and nephritis, and finally to chronic glomerulonephritis with nephrotic manifestations speaks strongly for a unitarian hypothesis in relation to the etiology and pathogenesis of this disease. It appears reasonable to believe that all the members of this family suffer from a single disease expressing itself in different ways, depending upon the duration and intensity of the nephrotic process. The results of the present studies support the conclusion of Barnett et al.[3] and Heymann et al.[30] that the nephrotic syndrome in children is basically a single disease which may or may not include manifestations of nephritis.

The clinical evidence for a unitarian hypothesis concerning the pathogenesis of nephrosis gains strong support from the pathologic findings in these cases.

Bell [31] focused attention on the glomerulus as the primary site of renal pathology in nephrosis, and most workers now regard the tubular changes as secondary to the alterations of glomerular function. In our four cases study of the biopsy material with the light microscope revealed normal architecture in Case 2 (transient nephrosis), minimal proliferation changes or no renal lesion in Case 4 ("pure" nephrosis), the proliferative changes characteristic of subacute glomerulonephritis in Case 3 (mixed nephrosis), and the severe scarring and proliferation characteristic of chronic glomerulonephritis in Case 1. Thus, virtually the whole pathologic spectrum known to be associated with the nephrotic syndrome was observed among the members of this one family, in which it can be presumed that a single pathogenic mechanism underlies the disease. These observations are consistent with the findings of other investigators who studied the pathology of sporadic nephrosis [31-36] and, as do the clinical studies, favor a unitarian concept of the etiology and pathogenesis of the nephrotic syndrome in childhood.

Further evidence supporting the unitarian hypothesis was obtained by examination of the kidney biopsies of the children of this family with the electron microscope. Indeed, an abnormality of the epithelial-cell layer of the glomerular capillary membrane, common to all the cases, was observed at the submicroscopic level in each of the children.[37]

Although the nephrotic syndrome observed in four siblings is indistinguishable in its clinical, physiologic, and pathologic manifestations from nephrosis occurring sporadically, several apparent differences deserve further comment.

Our observations on familial nephrosis agree with those of Fanconi,[5] who reported that (1) the familial form of the disease is severer and the prognosis is worse than that of sporadic nephrosis; (2) the familial nephrotic syndrome occurs at an earlier age than does sporadic nephrosis, and (3) the

TABLE 9.—*Therapy Attempted in Familial Nephrosis*

Patient	Infusions (Plasma or Albumin)	Infections Spontaneous	Hormone		HN_2 (0.4 Mg. in 2 Days)	Malaria	Typhoid Vaccine Fever
			Corticotropin (150 Mg./Sq. M.)	Cortisone (300 Mg./Sq. M.)			
Case 1	Numerous	Measles	× 6 days	.....	5 courses	P. vivax × 2 (no infection)	Fever × 20 days
Case 2	.....	.....	.....	.....	.....	.....	.....
Case 3	3 courses	Measles; chickenpox	× 10 days × 17 days	× 17 days	2 courses	P. ovale (no infection)	Fever × 20 days
Case 4	.....	.....	× 12 days	× 15 days	.....	.....	.....

HN_2 = mechlorethamine hydrochloride (nitrogen mustard).

familial nephrotic syndrome appears to be more resistant to treatment than sporadic nephrosis.

Although it may be true that familial nephrosis, in general, tends to have an earlier onset than sporadic nephrosis, this is not uniformly the case. For example, we have recently studied eight cases of sporadic nephrosis which had their onset during the first year of life,[38] and in one of the cases included in this report familial nephrosis had its onset as late as the fifth year of life.

It seems possible that the early onset of familial nephrosis, the poor prognosis, and the failure to respond to therapy are related, since the children with sporadic nephrosis whose disease began early in life similarly have had a poor prognosis and have been resistant to treatment. Indeed, it seems possible that failure to respond to therapy is a function of the severity of the disease.

The early onset of familial nephrosis (beginning on the first day of life in one of our cases) might be interpreted as evidence against the possibility that infection or a hypersensitivity reaction to infection play a significant role in the pathogenesis of the disease.

It is of course possible that although familial nephrosis and sporadic nephrosis are clinically and pathologically similar, as our studies indicate, their etiology and pathogenesis may differ.

Our failure to demonstrate circulating antibody to renal tissue in the serum of the mother of the children in this family may be interpreted as evidence that a mechanism other than immunity is involved in the etiology of the familial disease. A hereditary factor is suggested by the family history. Hereditary transmission of renal tubular disease is recognized,[39,40] and it seems possible that hereditary renal glomerular disease might occur. The delayed onset of familial nephrosis in Case 2 at 5 years of age, however, makes it necessary to postulate that if a hereditary factor is responsible for the familial disease its effect may be delayed by a period of at least 5 years.

Summary

A description of four cases of the nephrotic syndrome occurring in a single family is presented.

The clinical spectrum of the disease observed in this family included transient "pure" nephrosis, persistent "pure" nephrosis, so-called mixed nephrosis-nephritis, and chronic glomerulonephritis with the nephrotic syndrome.

Extensive investigation failed to reveal any fundamental difference between familial nephrosis and sporadic nephrosis.

Studies of the parents and a half brother of the involved children are presented, and the significance of maternal renal disease is considered.

Studies of biopsies of the kidney of each of the children revealed a pathologic spectrum ranging from normal renal tissue through intermediate stages of abnormality to advanced glomerulonephritis.

The hypothesis is presented that, originating within a single family, these four cases of nephrosis have a single etiology and pathogenesis.

The demonstration of a broad clinical and pathologic spectrum of the disease within a single family is presented as an argument favoring the unitarian concept of the nephrotic syndrome in childhood.

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Erythrocytes and Hemoglobin of the Blood in Infancy and Childhood

III. Factors in Variability, Statistical Studies

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This paper presents a summary of hematologic data collected during the years 1932 to 1942. Some have been published previously in reports dealing particularly with problems of iron-deficiency anemia.[1-5] At the time the studies were done plans were made for more complete statistical analysis of the assembled data, but various circumstances delayed the completion of that part of the project. The data are now presented in tables and charts designed to emphasize the sequence of changes in characteristics of the erythrocytes of infants and children at different ages and to demonstrate certain patterns of variability in those characteristics observed within different age groups.

The data were derived from studies on 1735 samples of blood from infants and children selected at random, at ages from birth to 16 years. Of these, 1568 samples were from children born at full term, of single birth, and 167 samples were from twins, triplets, and prematurely born infants. Data from the latter were tabulated separately. These infants were treated as a single group because hematologically they appeared to follow similar patterns. For brevity these infants are referred to as the "premature group." Only a single sample was drawn from some individual infants, but from others samples were drawn serially at varying intervals while the infants were followed closely during periods of time from two to five years or longer. The observations include samples from infants and children in the hospital, outpatient clinics, and orphanages, children both well and sick and from families of varying economic levels, but no patients with primary blood dyscrasias, and none who had ever received transfusions or any form of antianemic therapy. All were white, with known birth weight and birth order. Many studies on Negro infants were done but are not included in the present report because they did not represent a good sampling of the Negro population.

We believe the subjects included in the present report comprised a representative sample of the white infant and child population of Cincinnati. Although most of the data were gathered 20 years ago, current observations in the hospital and outpatient clinic indicate that the incidence of iron deficiency disclosed by the indices here described remains essentially unchanged.

Laboratory and Statistical Methods

All measurements were made in the research laboratory. Blood samples were drawn by vein puncture and delivered into heparinized vials from which the blood was taken for the various tests. Hematocrit measurements were made in quadruplicate by the capillary tube method of Guest and Siler.[7] For cell counting, duplicate dilutions were made in certified hemocytometer pipettes which were agitated mechanically. Double counting chambers were filled from each pipette, thus making quadruplicate counts for each blood sample. Hemoglobin was determined at first as carboxyhemoglobin by the Palmer method,[8] later as oxyhemoglobin, in a photoelectric colorimeter. Both methods were standardized by determinations of oxygen or

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carbon monoxide capacity by the Van Slyke method.[9] The indices of mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration (MCHC), and mean corpuscular hemoglobin (MCH) were calculated as usual, according to Wintrobe.[10]

Undoubtedly the least accurate measurement is the red cell count, but the errors inherent in counting were thoroughly studied and procedures were developed to reduce technical errors to a minimum. When technical errors are minimal the number of cells counted on each square of the counting chamber should be distributed in a Poisson series; the mean divided by the variance should be close to one (Fisher[11]). Random sampling of large numbers of our cell counts revealed values for the mean divided by variance satisfactorily close to this expected theoretical figure.

The assembled data were transferred to I. B. M. punch cards. A card was punched for each blood sample and repeated samples from the same child were identified by case number. Data from twins and premature infants were tabulated separately. The cards were sorted by age in days and by birth order. These data were printed on sheets in such a manner as to make them readily available for statistical calculations and for construction of tables and charts. All statistics were calculated directly from these printed sheets, thus avoiding the error due to grouping.

With the exception of blood samples taken at birth or during the first 10 days of life, our sampling was not initially planned on the basis of age. Samples were taken at random from infants and young children as they presented themselves. Very early in the study it became obvious that age was the most important variable in the interpretation of all findings. Therefore, for presentation and for statistical analysis, the samples were grouped in such a manner that the figures would best reflect the changing patterns. During the neonatal period, when changes are extremely rapid, the span for each group is short; after 3 months, when the changes are more gradual, the span is increased to two months; after 2 years it is increased to six months, and finally to a year or longer. These groupings appear reasonably satisfactory for purposes of the analysis, with the possible exception of those for the first few days of life.

The arithmetical mean, or average, is presented in the tables and charts as a measure of central tendency. In age groups in which a certain degree of stability has been achieved, as at 6 months, or again at 3 years, the arithmetical mean is a satisfactory figure, but in periods when values are changing rapidly it must be regarded more critically. During the periods in which variability was greatest we were forced to conclude that no statistic would adequately describe the situation. In most

Data from 1241 samples of blood from infants and children, 3 months to 14 years

Hematocrit versus Hemoglobin — **Red Cell Counts versus Hemoglobin**

Totals	Hematocrit per cent (midpoints of groups) 16 18 20 22 24 26 28 30 32 34 36 38 40 42 44 46 48 50	Hemoglobin in Whole Blood gm./100cc	Red Cell Count M/c mm (midpoints of groups) 25 27 29 31 33 35 37 39 41 43 45 47 49 51 53 55 57 59 61	Totals
1	1	4.0	1	1
4	2 2	5.0	1 1 1 1	4
2	1 1	6.0	1 1	2
7	2 3 2	7.0	1 1 2 1 1 1	7
12	3 4 3 1 1	8.0	1 2 2 1 2 2 2	12
40	1 2 17 14 5 1	9.0	1 1 2 3 3 1 5 3 3 4 1 7 2 1 3	40
88	1 11 29 44 3	10.0	3 3 6 9 5 10 7 8 9 12 11 3 1 1	88
170	2 25 79 58 6	11.0	1 1 4 11 28 29 26 20 17 11 8 8 2 3 1	170
343	4 46 184 99 10	12.0	1 8 27 59 66 75 40 39 14 4 5 4 1	343
342	1 38 97 96 9 1	13.0	3 5 32 70 94 61 42 21 7 5 1 1	342
184	1 1 25 106 45 6	14.0	2 6 14 31 48 37 31 6 8 1	184
43	1 2 22 16 2	15.0	1 2 5 8 8 9 5 4 1	43
3	1 1 1	16.0	1 1 1	3
2	1 1	17.0	1 1	2
1241	1 0 2 2 3 9 8 33 73 77 285 329 257 62 24 3 0 2	← Totals →	1 0 2 1 5 5 15 38 74 143 191 299 187 157 95 40 28 12 8	1241

HIGH DEGREE OF CORRELATION $r = .896$ LOW CORRELATION $r = .397$

Fig. 1.—Correlations of values for hemoglobin in whole blood—hematocrit and red cell counts.

cases, however, the use of the arithmetical mean does not seriously distort the facts and we have used it as the most familiar form of average. It must, however, be borne in mind that in many age groups the average figure does not represent expected normal values. Standard deviations are presented as a measure of variability within each group. In all tests of significance a probability of 5 in 100 (P=0.05) or less was accepted according to convention as indicating a significant difference.

Figure 1 serves to emphasize the relative importance of and interrelationships between the three directly determined values. Data on 1241 samples of blood from infants and children from 3 months to 14 years of age are arranged for comparison of the values for hemoglobin with corresponding values for hematocrit and red cell counts. The table demonstrates a high degree of positive correlation (r=0.896) between the hematocrit and hemoglobin values. Far less correlation exists between the red cell counts and the hemoglobin values (r=0.397). It is obvious that high cell counts were frequently associated with low hemoglobin values. In more than 25% of samples with hemoglobin content less than 11.5 gm. per 100 cc., the corresponding red cell count was 5,000,000 or more. Thus, in all of these samples the MCH values were 23γγ or less, indicating moderate to severe hypochromia. One must conclude, therefore, that the cell count taken alone often is not informative and may even be very misleading as an index of anemia, particularly at ages when iron-deficiency anemias are most frequently encountered. Hemoglobin in whole blood has been traditionally used as an index of anemia, but when the red cell count is high both hematocrit and hemoglobin in whole blood may be close to the expected normal levels even in the presence of moderately severe iron deficiency. None of the three direct measurements is as informative with regard to iron-deficiency states as the three calculated indices MCV, MCHC, and MCH, which give quantitative indications of microcytosis and hypochromia.

Presentation of Data and Comment

Figures presented in Table 1 indicate clearly that the incidence of iron-deficiency anemia among infants of our community is about the same today as it was 20 years ago, when the data analyzed in the present paper were collected. Recently, Dr. M. E. Lahey [6] summarized hematologic data on 1500 children successively admitted to the Cincinnati Children's Hospital in 1954. All children whose hemoglobin was less than 10.5 gm. per 100 cc. of whole blood were thoroughly studied. Among 314 children between the ages of 6 months and 3 years, 69, or 22%, were positively diagnosed as having iron-deficiency anemia after anemias due to bleeding or chronic diseases were excluded. During the years of our study, 1932 to 1942, 123, or 20%, of 613 children of the same age group were classified as having anemia of iron deficiency, with levels of hemoglobin in whole blood less than 10.5 gm. per 100 cc.

Full-Term and Premature Infants.—Table 2 summarizes data on 1568 samples of blood from infants and children at ages from birth to 16 years. For each of the 25 age groups figures are given for the mean values for hematocrit, red cell counts, and hemoglobin, and the three calculated indices MCV, MCHC, and MCH, with the respective standard deviations and standard errors.

In Tables 3 to 8 frequency distributions of the various values are listed, grouped by age as in Table 2. Among the figures for frequencies, bold face type indicates the approximate position of the mean within each age group. Note that the widest ranges of values occur in the neonatal period and at about 18 months, while the narrowest ranges occur at about 3 to 6 months and again at 3 years.

The same patterns of variation with age are demonstrated graphically in the scatter

TABLE 1.—*Incidence of Anemia Probably Due to Iron Deficiency in Infants of Cincinnati; Observations by M. E. Lahey, 1954 and by Ourselves in 1932-1942*

Age	1954 Number of Observations			1932–1942 Number of Observations		
	Total	Hb Less than 10.5 Gm/100 Cc.	Per Cent	Total	Hb Less than 10.5 Gm/100 Cc.	Per Cent
6 mo. to 1 yr.	74	18	24.3	180	35	19.4
1 yr. to 2 yr.	140	42	30.0	295	78	26.4
2 yr. to 3 yr.	100	9	9.0	138	10	7.2
Total	314	69	22.0	613	123	20.1

TABLE 2.—*Data on 1568 Samples of Blood of Infants and Children at Ages from Birth to Sixteen Years*

Age Span in Days	Midpoint Age	No. of Cases	Red Blood Cells					Hemoglobin					
			Volume per Cent		Count, $\overline{M}$/Cu. Mm.		MCV, Cu. μ	$\sigma \pm$ SE.	In Whole Blood Gm. per 100 Cc.		In Cells, MCHC, Gm. per 100 Cc.		Per Cell, MCH, $\gamma\gamma$	
			Mean $\pm$ SE$_m$	$\sigma \pm$SE.	Mean $\pm$SE$_m$	$\sigma \pm$SE.	Mean $\pm$ SE$_m$		Mean $\pm$ SE$_m$	$\sigma \pm$SE$_m$	Mean $\pm$ SE$_m$	$\sigma \pm$SE.	Mean $\pm$ SE$_m$	$\sigma \pm$SE$_m$
Cord Blood	Cord Blood	59	52.3±0.7	5.3±0.5	4.638±0.064	0.495±0.046	113±0.8	6.1±0.6	17.1±0.23	1.78±0.16	32.6±0.18	1.41±0.13	36.9±0.28	2.16±0.20
<2	1 day	59	58.2±0.9	6.6±0.6	5.305±0.072	0.555±0.051	110±0.7	5.6±0.5	19.4±0.28	2.14±0.20	33.5±0.17	1.29±0.12	36.6±0.25	1.89±0.17
2-3.9	3 days	47	54.5±0.8	6.3±0.6	5.060±0.088	0.603±0.062	108±1.0	6.8±0.7	18.5±0.32	2.16±0.22	33.9±0.19	1.32±0.14	36.7±0.39	2.67±0.28
4-9.9	7 days	66	54.9±0.8	6.2±0.5	5.216±0.077	0.628±0.055	106±0.6	5.0±0.4	18.8±0.26	2.13±0.19	34.3±0.18	1.43±0.12	36.2±0.30	2.42±0.21
10-29	20 days	42	46.2±1.1	7.2±0.8	4.640±0.113	0.730±0.080	100±0.8	5.3±0.6	15.9±0.36	2.33±0.25	34.5±0.25	1.60±0.17	34.4±0.32	2.07±0.23
30-60	45 days	46	36.5±0.7	4.8±0.5	3.874±0.074	0.501±0.053	94±0.8	5.6±0.6	12.7±0.24	1.64±0.17	34.9±0.16	1.11±0.12	32.8±0.29	1.98±0.21
61-90	76 days	60	33.1±0.3	2.6±0.2	3.766±0.044	0.344±0.031	88±0.6	4.9±0.4	11.4±0.12	0.96±0.09	34.6±0.16	1.27±0.12	30.4±0.21	1.63±0.15
91-151	122 days	71	35.3±0.4	3.1±0.3	4.332±0.061	0.511±0.043	82±0.7	5.7±0.5	11.9±0.12	1.02±0.09	33.7±0.17	1.43±0.12	27.7±0.26	2.23±0.19
152-212	6 mo.	62	34.8±0.3	2.5±0.2	4.483±0.052	0.412±0.037	78±0.7	5.2±0.5	11.6±0.12	0.98±0.09	33.5±0.20	1.59±0.14	26.1±0.28	2.23±0.20
213-273	8 mo.	64	35.6±0.4	3.2±0.3	4.713±0.063	0.503±0.044	76±0.7	5.8±0.5	11.7±0.17	1.32±0.12	32.8±0.22	1.72±0.15	24.9±0.33	2.66±0.24
274-334	10 mo. –	57	34.9±0.4	2.8±0.3	4.834±0.058	0.440±0.041	73±1.0	7.8±0.7	11.3±0.18	1.35±0.13	32.4±0.28	2.12±0.20	23.7±0.47	3.57±0.33
335-394	12 mo.	51	34.5±0.6	4.1±0.4	4.758±0.072	0.515±0.051	73±1.1	7.7±0.8	11.1±0.24	1.71±0.17	32.3±0.32	2.32±0.23	23.5±0.51	3.65±0.36
395-455	14 mo.	53	34.6±0.5	3.7±0.4	4.700±0.074	0.542±0.053	74±1.0	7.6±0.7	11.1±0.25	1.80±0.17	31.8±0.37	2.69±0.26	23.8±0.51	3.74±0.36
456-516	16 mo.	50	34.7±0.5	3.4±0.3	4.904±0.073	0.517±0.052	71±1.2	8.5±0.8	11.0±0.22	1.58±0.16	31.7±0.31	2.20±0.22	22.8±0.55	3.90±0.39
517-577	18 mo.	53	34.8±0.4	2.9±0.3	4.868±0.062	0.450±0.044	72±1.2	8.7±0.8	11.2±0.27	1.97±0.19	31.9±0.39	2.83±0.28	23.2±0.60	4.38±0.43
578-638	20 mo.	47	35.9±0.4	3.1±0.3	4.807±0.072	0.496±0.051	75±1.1	7.3±0.8	11.7±0.22	1.49±0.15	32.6±0.31	2.14±0.22	24.6±0.52	3.58±0.37
639-820	2 yr.	103	35.8±0.3	3.0±0.2	4.777±0.042	0.429±0.030	75±0.7	7.3±0.5	11.7±0.14	1.47±0.10	32.6±0.21	2.16±0.15	24.7±0.35	3.59±0.25
821-1003	2.5 yr.	74	36.2±0.3	3.0±0.2	4.703±0.041	0.354±0.029	77±0.7	5.9±0.5	12.1±0.16	1.40±0.12	33.5±0.22	1.90±0.16	25.9±0.35	3.02±0.25
1004-1185	3 yr.	56	36.6±0.4	2.8±0.3	4.691±0.052	0.392±0.037	78±0.7	5.0±0.5	12.4±0.15	1.14±0.11	34.0±0.20	1.49±0.14	26.6±0.28	2.69±0.20
1186-1368	3.5 yr.	49	37.3±0.3	2.1±0.2	4.771±0.055	0.384±0.039	78±0.7	4.8±0.5	12.6±0.13	0.89±0.09	33.9±0.18	1.29±0.13	26.6±0.31	2.18±0.22
1369-1550	4 yr.	43	36.9±0.4	2.9±0.3	4.618±0.051	0.331±0.036	80±0.8	5.0±0.5	12.4±0.21	1.38±0.15	33.7±0.27	1.77±0.19	26.9±0.41	2.69±0.29
1551-2098	5 yr.	97	37.2±0.3	2.5±0.2	4.651±0.047	0.464±0.033	80±0.4	3.8±0.3	12.7±0.10	1.01±0.07	34.2±0.12	1.18±0.08	27.5±0.15	1.50±0.11
2099-3010	7 yr.	103	38.1±0.4	3.7±0.3	4.790±0.051	0.518±0.036	79±0.9	9.2±0.6	12.9±0.18	1.87±0.13	34.3±0.13	1.34±0.09	27.4±0.20	2.07±0.14
3011-4288	10 yr.	111	38.5±0.3	2.8±0.2	4.804±0.045	0.477±0.032	81±0.6	6.3±0.4	13.2±0.12	1.22±0.08	34.3±0.14	1.46±0.10	27.6±0.26	2.73±0.18
4289-5030	14 yr.	45	39.7±0.5	3.3±0.4	4.922±0.077	0.519±0.055	81±1.1	7.4±0.8	13.6±0.22	1.46±0.15	34.3±0.27	1.81±0.19	27.9±0.48	3.25±0.34

TABLE 3.—*Packed Cell Volume (Hematocrit); Frequency Distributions at Different Ages—Full-Term Single Births*

Per Cent	Cord Blood	Midpoint of Age Groups: Days 1	3	7	20	45	76	122	Months 6	8	10	12	14	16	18	20	Years 2	2.5	3	3.5	4	5	7	10	14
72–73.9			1																						
70–71.9		2																							
68–69.9	1	1																							
66–67.9	1	6		2	1																				
64–65.9		4	1	3																					
62–63.9		5	6	6																					
60–61.9	2	6	2	7																					
58–59.9	3	**10**	3	5	1																				
56–57.9	9	6	6	8																					
54–55.9	8	6	**7**	**10**	2																				
52–53.9	**10**	3	7	4	5																				
50–51.9	5	4	4	7	6																		1		
48–49.9	9	3	4	5	2																		1		
46–47.9	6	1	3	3	**6**	1																1	2		4
44–45.9	3	1	1	3	5	2		1		1						1						1	9	13	11
42–43.9	2		2	3	4	6	1	1		1	1				1			2	1	2					
40–41.9					4	2		4	1	5	2	4	4	1	5	4	5	6	4	2	9	13	18	24	12
38–39.9		1			2	9	1	12	6	11	6	4	6	10	7	11	21	15	18	20	10	32	**36**	**45**	**9**
36–37.9					2	**5**	6	12	19	10	15	16	15	10	11	15	38	**22**	**18**	**19**	**15**	**29**	17	18	3
34–35.9					1	8	**24**	**22**	**18**	**18**	**18**	**9**	**12**	**14**	**13**	**9**	**23**	20	8	3	4	15	12	9	2
32–33.9						6	**11**	13	10	7	9	11	8	9	9	5	10	6	3	3	3	4	3	1	4
30–31.9						5	11	5	7	8	5	5	4	3	3	1	2		3		1	1	1		
28–29.9						1	6	1	1	2			1	2	1	1	2	1	1			1	1		
26–27.9						1					1	1	1		2			2			1		1		
24–25.9					1								1			1	1								
22–23.9													1		1								1		
20–21.9														1			1								
18–19.9																								1	
16–17.9																									
14–15.9												1													
Total	59	59	47	66	42	46	60	71	62	64	57	51	53	50	53	47	103	74	56	49	43	97	103	111	45

TABLE 4.—*Red Blood Cell Counts; Frequency Distributions at Different Ages—Full-Term Single Births*

Millions per Cu. Mm.	Cord Blood	Midpoint of Age Groups																						
		Days							Months								Years							
		1	3	7	20	45	76	122	6	8	10	12	14	16	18	20	2	2.5	3	3.5	4	5	7	10	14
6.8–6.99		1																						
6.6–6.79					1																			
6.4–6.59			2	1																				
6.2–6.39		3		2																				
6.0–6.19		4	3	4							2			1		1						2	2	
5.8–5.99	1	1	1	4	1						1			3	1		1			1		1	1	2
5.6–5.79		7	2	12	3			1		3	2	2	2	2	1	3	4			1		1	2	3
5.4–5.59	4	9	3	7				1	1	4		2	1	3	4	2	6	1	2			5	5	2
5.2–5.39	3	8	6	4	6			2		3	2	3	7	5	8	5	7	6	4	6	1	6	10	9	8
5.0–5.19	4	7	10	10	1			4	9	9	10	12	6	7	10	2	12	10	6	5	5	13	14	15	4
4.8–4.99	10	9	6	4	2	1		5	4	10	13	8	11	4	6	9	13	12	8	9	7	13	17	21	9
4.6–4.79	9	8	3	4	6	3	1	8	10	9	14	7	3	10	7	8	24	18	14	9	8	23	21	26	8
4.4–4.59	7	1	5	6	6	4	1	5	12	9	4	9	9	8	7	8	18	9	9	12	11	17	18	12	3
4.2–4.39	9		4	5	6	4	6	15	12	5	7	2	4	3	6	4	11	13	8	5	5	18	6	10	3
4.0–4.19	7		1	1	4	7	8	11	6	8	1	2	5	3	2	5	6	4	3		5	3	3	3	1
3.8–3.99	3			2	2	8	7	11	6	2	1	2	1	1	1			1	2	1	1	4	1	3	
3.6–3.79	2		1		2	6	21	3	1	2		1	3				1						2	1	1
3.4–3.59		1			1	6	6	2	1																1
3.2–3.39						3	9	3															1		
3.0–3.19						1	1						1												
2.8–2.99						3						1												1	
2.6–2.79					1																				
2.4–2.59																							1		
Total	59	59	47	66	42	46	60	71	62	64	57	51	53	50	53	47	103	74	56	49	43	97	103	111	45

TABLE 5.—*Mean Corpuscular Volume (MCV); Frequency Distributions at Different Ages—Full-Term Single Births*

Cubic Microns	Cord Blood	Midpoint of Age Groups																						
		Days							Months								Years							
		1	3	7	20	45	76	122	6	8	10	12	14	16	18	20	2	2.5	3	3.5	4	5	7	10	14
126–129.9	1																								
122–125.9	1	2	1																						
118–121.9	16	2																							
114–117.9	12	8	10	2																					
110–113.9	14	19	12	15	1	1																			
106–109.9	9	19	10	18	2	1																			
102–105.9	5	4	6	15	10	3																			
98–101.9		4	5	12	14	4	3																		
94– 97.9		1		3	9	17	3	2															1	3	2
90– 93.9	1		2	1	5	10	14	5	1			1		1	1				1				1	7	5
86– 89.9			1		1	8	25	10	3	2	1	2	4			3	4	2	3	2	3	6	6	9	5
82– 85.9						2	12	20	12	11	7	5	5	4	5	4	11	15	8	11	12	35	31	29	9
78– 81.9							2	19	18	13	8	6	8	8	9	14	34	26	19	16	17	32	35	30	12
74– 77.9							1	10	16	14	14	10	14	8	11	9	20	17	15	12	9	21	19	20	9
70– 73.9								4	9	13	10	8	6	6	7	5	10	7	8	6		2	7	9	
66– 69.9								1	2	8	8	10	8	10	8	6	4	3	1	2	1	1	3	1	
62– 65.9										3	5	6	2	6	3	4	8	1	1					2	2
58– 61.9									1		1	2	5	4	4	2	2	3			1			1	1
54– 57.9											2	1	1	2	4		4								
50– 53.9											1			1	1										
Total	59	59	47	66	42	46	60	71	62	64	57	51	53	50	53	47	103	74	56	49	43	97	103	111	45

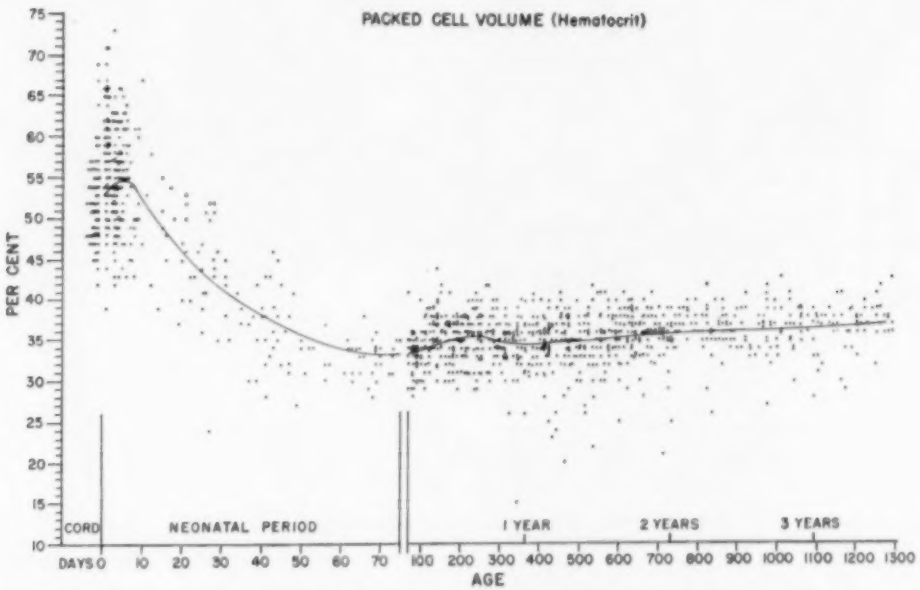

Fig. 2.—Packed cell volume (hematocrit) in cord blood and in blood drawn from infants at ages from birth to 3½ years. In this and in the following scatter charts note the change of scale for age after the neonatal period of 76 days.

charts, Figures 2 to 7, where each dot represents a single observation. In these charts the smoothed curves indicate approximately the position of the mean values. In the charts the scale representing the first 76 days is broadened to emphasize the striking changes characteristic of the neonatal period. The distribution of the dots in Figures 4 and 7 shows especially clearly the high incidence of microcytosis and hypochromia, indicating iron deficiency, apparent at the end of the first year and greatest during the second year. The horizontal alignment of the dots in Figures 2 and 4 resulted from dropping figures after the decimal point.

Data on the 167 samples of blood from the "premature group" are listed in Table 9, arranged in the same manner as in Table 2, and frequency distributions of these values are listed in Tables 10-15. In these tables the patterns of changes immediately following birth are not shown so clearly as for the full-term group because fewer blood samples were drawn from the small premature infants and the age groupings were made broader.

In Figure 8 smoothed curves represent mean values at different ages for the full-term and the premature infants. During the period from birth to about 3 months of age there was no significant difference in the average hematologic values between the full-term and premature infants; even afterward, there was no significant difference between average red cell counts in the two groups. From 3 months on, however, the values for hematocrit, hemoglobin in whole blood, and size and hemoglobin content of the red cells in the premature group followed a more rapid downward course. At about 8 months of age the premature infants had an average of only 8.7 gm. of hemoglobin per 100 cc. of whole blood; all had microcytosis and very low hemoglobin indices, MCHC and MCH (Table 9).

The curves in Figure 8 representing averages in the "premature" groups would of course have fallen to lower levels had not

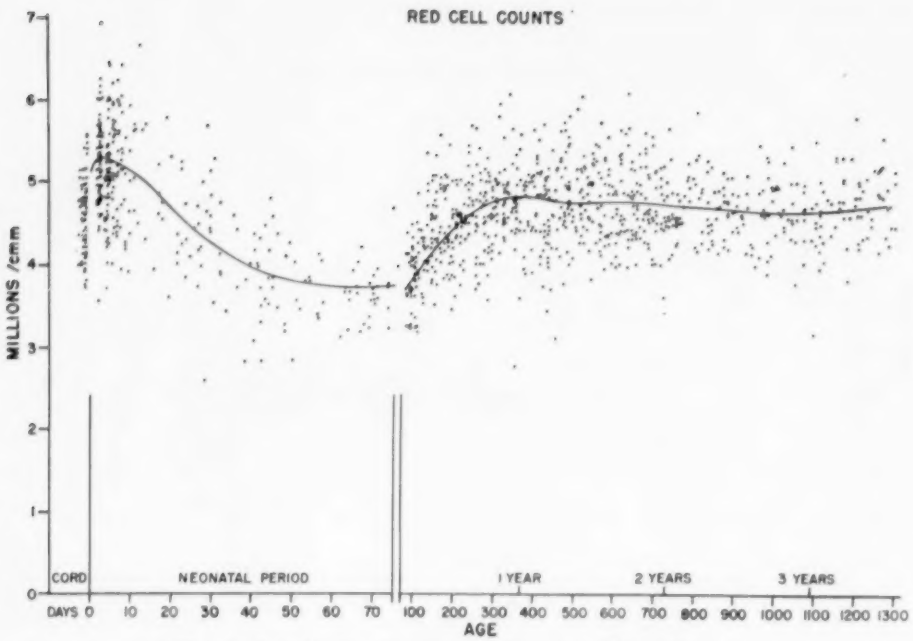
RED CELL COUNTS
MILLIONS /cmm
CORD
NEONATAL PERIOD
1 YEAR
2 YEARS
3 YEARS
DAYS 0 10 20 30 40 50 60 70 100 200 300 400 500 600 700 800 900 1000 1100 1200 1300
AGE

Fig. 3.—Red blood cell counts—millions per cubic millimeter.

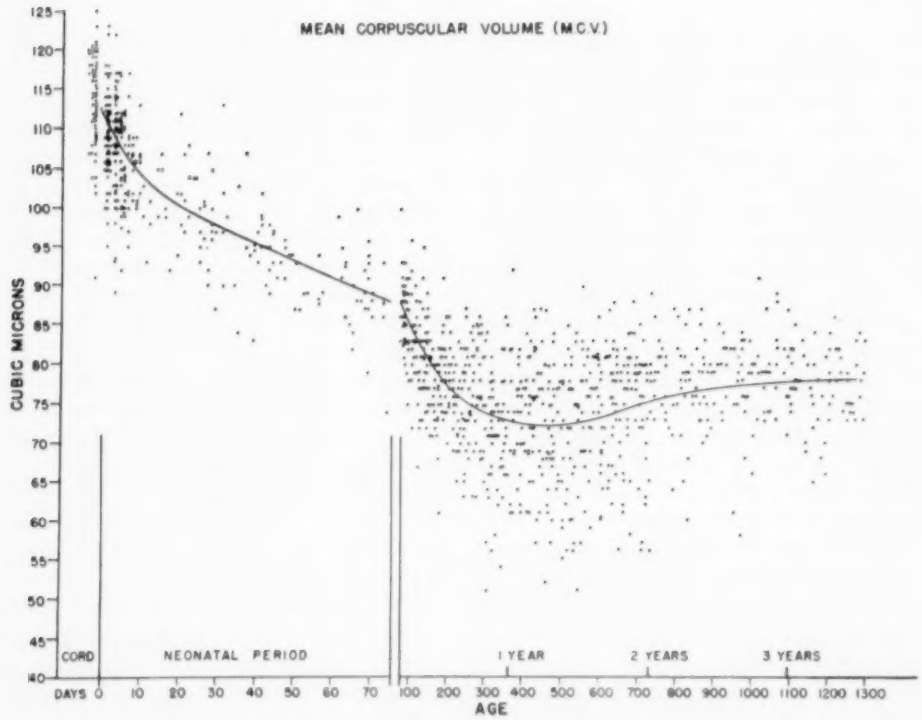
MEAN CORPUSCULAR VOLUME (MCV)
CUBIC MICRONS
CORD
NEONATAL PERIOD
1 YEAR
2 YEARS
3 YEARS
DAYS 0 10 20 30 40 50 60 70 100 200 300 400 500 600 700 800 900 1000 1100 1200 1300
AGE

Fig. 4.—Mean corpuscular volume (MCV), cubic microns.

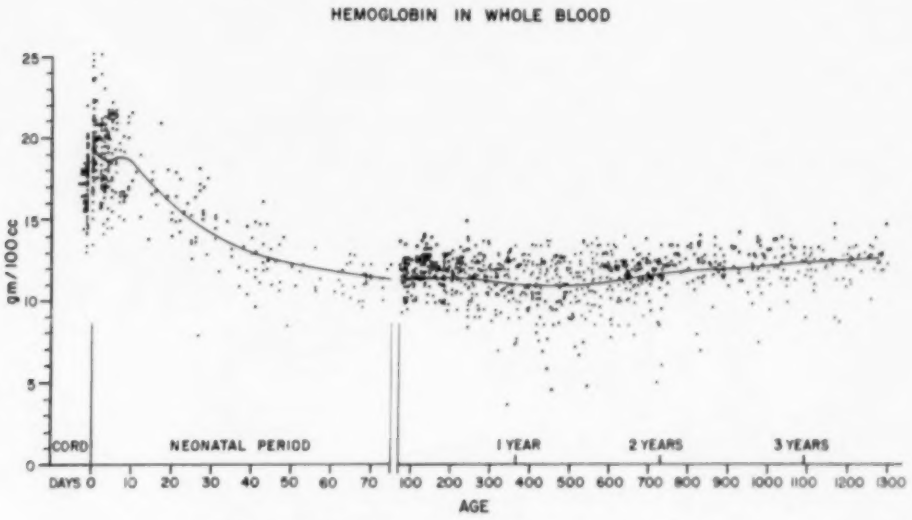

Fig. 5.—Hemoglobin in whole blood, grams per 100 cc.

many of the prematures been treated with iron. When the values were found approaching anemic levels, therapy was started, and subsequently these infants were omitted from the series of untreated cases upon which this chart is based. The effects of iron therapy were amply discussed in earlier reports.

Variability at Different Ages.—The postnatal period is a time of great variability in the blood values, both in individuals and between members of a group. At any given moment, until such time as the fetal type of cell has been replaced by the adult type, we may expect that each blood sample will contain cells of both types in varying proportions. Each average computed on a given group, therefore, will be a figure based not necessarily on the so-called normal curve of error, but on a curve which may be skewed to the left or to the right or even at times on a U-shaped curve of distribution. Each age group during this period contains individuals in which the process of cell replacement is more or less complete.

The immediate postnatal period, 1-48 hours, is characterized by rapid changes in the blood picture, as indicated in Table 2. In the group of full-term infants, hematocrit values increased from an average in cord blood of 52% to an average of 58% at one day and then slowly decreased to about 33% at 2 to 3 months. The average red cell count rose from 4,600,000 in cord blood to 5,300,000 at one day. The average count remained at 5,000,000 or more for the first 10 days and then decreased to reach a low figure of 3,700,000 at 2 to 3 months. Average values for hemoglobin in whole blood increased from 17.1 gm. per 100 cc. in cord blood to 19.4 gm. at one day, remained close to 19 gm. per 100 cc. for the first 10 days, and then decreased to 12.7 gm. at 2 to 3 months. During this period the average values for MCV and MCH steadily decreased and MCHC steadily increased until at about 3 months each of the three calculated figures approached the expected "normal" adult values. Values for hematocrit, red cell count, and hemoglobin in whole blood, however, were well below expected adult levels. At this time the majority of the infants exhibited some degree of anemia of the normochromic, normocytic type. The initial increases in values and the subsequent decreases are of decided statistical significance (P is less than 0.001 in almost every instance). These trends in red cell count

TABLE 6.—*Hemoglobin in Whole Blood; Frequency Distributions at Different Ages—Full-Term Single Births*

Grams per 100 Cc.	Cord Blood	Midpoint of Age Groups																							
		Days							Months								Years								
		1	3	7	20	45	76	122	6	8	10	12	14	16	18	20	2	2.5	3	3.5	4	5	7	10	14
25–25.9			1																						
24–24.9																									
23–23.9		3	1																						
22–22.9	1	3		1																					
21–21.9		7	2	14	1																				
20–20.9	2	10	8	9	1																				
19–19.9	4	**13**	7	10	1																				
18–18.9	13	10	**6**	**6**	1																		1		
17–17.9	**10**	5	11	7	10																	1	1		1
16–16.9	13	5	5	10	6	1																	1	3	6
15–15.9	9	2	4	6	**10**	2				1															
14–14.9	5		2	1	5	8		3		1					1	1	1	4	3	3	2	7	22	21	14
13–13.9	2	1			4	9	2	6	6	7	5	5	6	1	9	10	12	14	14	12	13	34	37	**45**	**12**
12–12.9					2	**11**	17	18	20	21	17	14	12	15	13	17	42	**29**	**24**	**25**	**17**	**39**	**25**	31	6
11–11.9						8	**24**	**31**	**21**	**16**	**14**	**12**	**12**	**14**	**9**	**7**	**28**	19	11	7	6	11	8	7	2
10–10.9						5	13	12	10	12	11	12	12	9	8	7	10	2	2	2	3	4	5	3	3
9– 9.9						1	4	1	5	5	8	5	4	7	7		4	3	1			1	2		1
8– 8.9						1				2	1	1	3	3	2	4	3	1	1		1				
7– 7.9					1						1	1	2		2	1	1	3			1		1		
6– 6.9													1		1		1								
5– 5.9													1				1								
4– 4.9														1	1									1	
3– 3.9												1													
Total	59	59	47	66	42	46	60	71	62	64	57	51	53	50	53	47	103	74	56	49	43	97	103	111	45

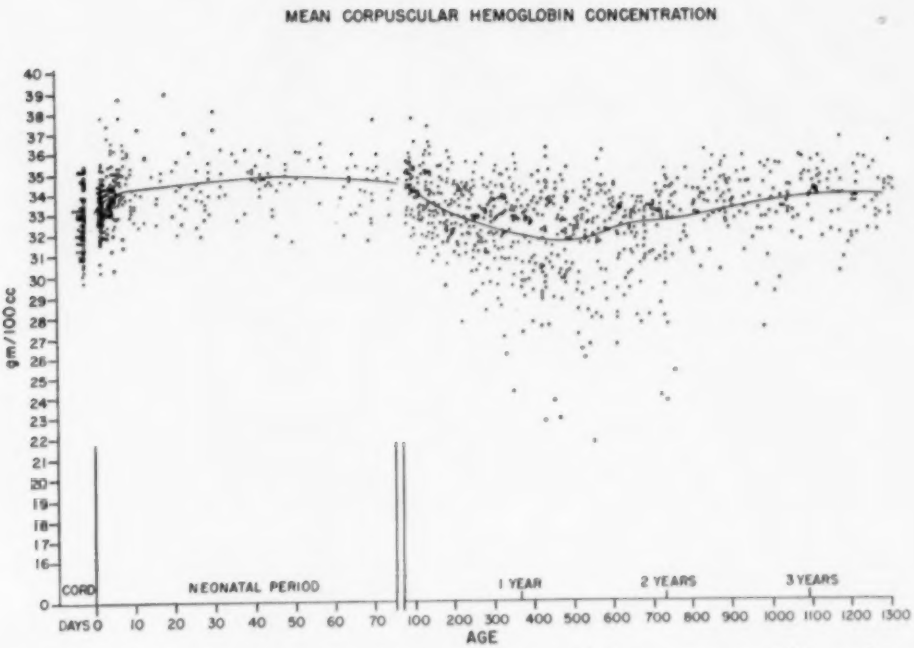
MEAN CORPUSCULAR HEMOGLOBIN CONCENTRATION
gm/100 cc
CORD
NEONATAL PERIOD
1 YEAR
2 YEARS
3 YEARS
DAYS 0 10 20 30 40 50 60 70 100 200 300 400 500 600 700 800 900 1000 1100 1200 1300
AGE

Fig. 6.—Mean corpuscular hemoglobin concentration (MCHC), grams per 100 cc. of packed cells.

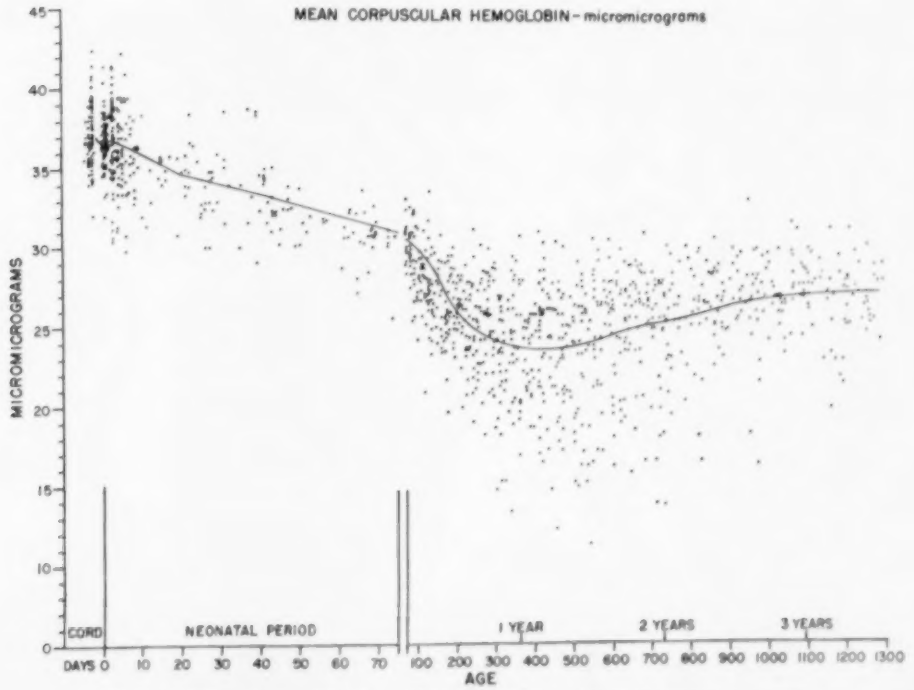
MEAN CORPUSCULAR HEMOGLOBIN - micromicrograms
MICROMICROGRAMS
CORD
NEONATAL PERIOD
1 YEAR
2 YEARS
3 YEARS
DAYS 0 10 20 30 40 50 60 70 100 200 300 400 500 600 700 800 900 1000 1100 1200 1300
AGE

Fig. 7.—Mean corpuscular hemoglobin (MCH), micromicrograms per cell.

TABLE 7.—*Mean Corpuscular Hemoglobin Concentration (MCHC); Frequency Distributions at Different Ages—Full-Term Single Births*

Grams per 100 Cc. Packed Cells	Cord Blood	Midpoint of Age Groups: Days 1	3	7	20	45	76	122	Months 6	8	10	12	14	16	18	20	Years 2	2.5	3	3.5	4	5	7	10	14
39-39.9				1	1				1														1		1
38-38.9		1		1	1		2									1								1	1
37-37.9			3	1	3	1		3											1	1	1	3	4	3	
36-36.9		2	3	6	4	13	9	5	5	3	1	2	1		2		1	7	7	5	2	10	11	14	7
35-35.9	8	9	4	19	9	21	23	12	9	8	7	4	6	3	5	5	12	18	15	10	12	24	31	33	13
34-34.9	7	14	20	**24**	**12**	**5**	**13**	18	15	9	13	9	13	5	9	11	29	18	**16**	13	14	**40**	**31**	**35**	**12**
33-33.9	17	**24**	**12**	9	9	4	10	**19**	**15**	19	9	17	3	12	11	14	23	**17**	9	**13**	**6**	12	17	16	5
32-32.9	**13**	7	4	3	3	2	3	11	12	**13**	**9**	**3**	7	12	11	**5**	**11**	5	5	7	3	7	6	5	4
31-31.9	11	1	1	1				3	4	6	9	5	**8**	**3**	**1**	3	15	4	1		3	1	2	3	1
30-30.9	3	1		1					1	3	4	6	6	10	3	3	4	1	2						
29-29.9										2	2	2	5	2	3	2	1	1			1				
28-28.9										1	1	1	2	1	4	2	5	2			1				1
27-27.9											1	1		1	2	1		1						1	
26-26.9											1				1										
25-25.9																									
24-24.9												1	1				2								
23-23.9													1	1											
22-22.9															1										
Total	59	59	47	66	42	46	60	71	62	64	57	51	53	50	53	47	103	74	56	49	43	97	103	111	45

TABLE 8.—*Mean Corpuscular Hemoglobin (MCH); Frequency Distribution at Different Ages—Full-Term Single Births*

Micro-micrograms	Cord Blood	Midpoint of Age Groups: Days 1	3	7	20	45	76	122	Months 6	8	10	12	14	16	18	20	Years 2	2.5	3	3.5	4	5	7	10	14
42-43.9	2	1	1	1																					
40-41.9	4	1	4	5																					
38-39.9	16	16	16	14	3	2																			
36-37.9	**21**	**28**	**10**	**22**	9																				
34-35.9	14	14	11	17	**15**	12	2																	4	
32-33.9	2	2	2	3	12	**24**	10	3												1	1	1	4	2	5
30-31.9			3	4	3	7	**35**	9	2	3	1	1	2	2	1	2	3	3	3	2	2	4	7	11	10
28-29.9						1	10	25	16	10	7	7	6	2	7	7	15	20	13	15	17	**48**	**40**	**45**	12
26-27.9							2	**24**	**18**	15	14	8	14	9	13	17	32	28	**28**	**16**	**16**	**32**	**34**	**35**	**12**
24-25.9							1	8	21	**18**	10	11	9	11	7	**7**	**24**	**13**	7	12	5	11	15	7	2
22-23.9								1	5	14	**11**	**8**	**7**	**8**	**10**	3	12	3	4	1		1	3	4	1
20-21.9								1	2	5	7	9	7	9	3	5	6	2	1	2	1			1	2
18-19.9										1	4	5	4	7	3	5	6	3						1	
16-17.9												1	3	2	6	1	3	2			1			1	1
14-15.9											3		1	1	2		1								
12-13.9												1		1			1								
10-11.9															1										
Total	59	59	47	66	42	46	60	71	62	64	57	51	53	50	53	47	103	74	56	49	43	97	103	111	45

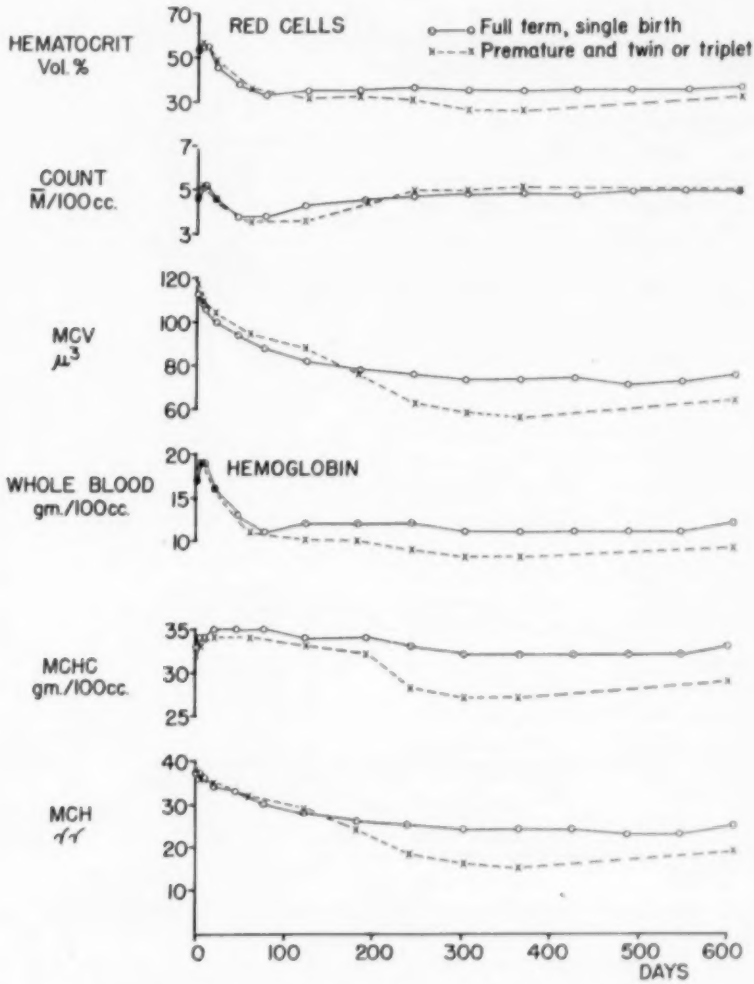

Fig. 8.—Curves represent averages of the several blood values among full-term and premature infants at different ages from birth to 600 days.

and the indices MCV, MCHC, and MCH during the first 76 days are represented graphically in Figure 9.

Figure 9 portrays the effects of new cells entering the circulation and the disappearance of fetal cells. The large fetal cells are moderately hypochromic, indicated by the average MCHC values of about 32.5 gm. per 100 cc. at birth. While the average red cell count rose sharply after birth the MCV values decreased, even during the first few neonatal hours. Concomitantly the values for MCH fell while the values for MCHC rose as normochromic cells entered the circulation in increasing numbers, finally replacing the large hypochromic cells of fetal life. At 30 to 60 days the fetal type of cells have largely disappeared and the circulating cells are mostly of the mature, adult type. At between 60 and 90 days the average figures for hematocrit, 33.1%, and red cell count, 3,770,000, were the lowest found in any age group. Subsequently the average values for hematocrit and red cell count

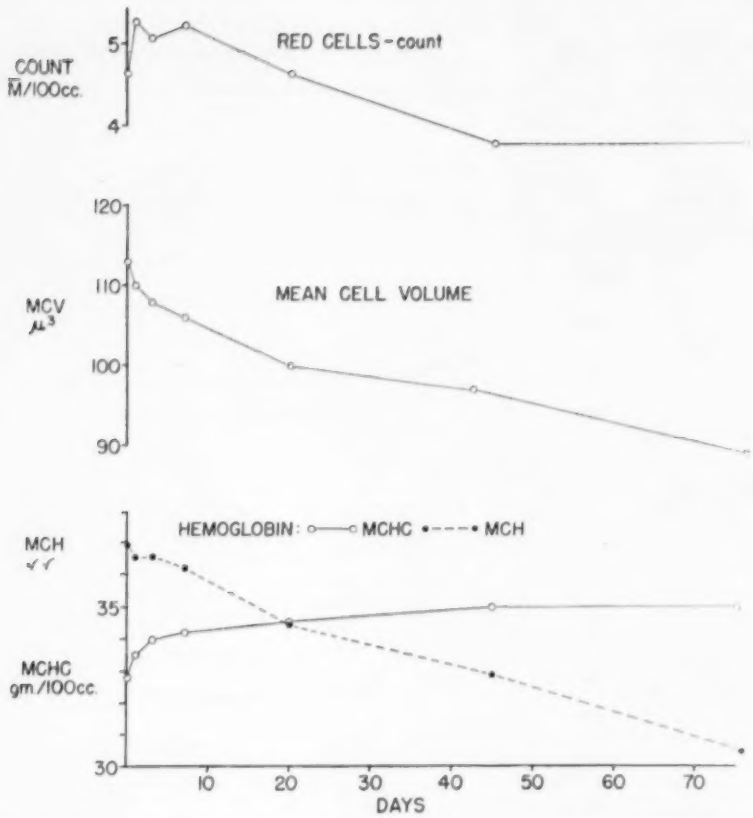

Fig. 9.—Curves represent average values for red cell count, MCV, MCHC, and MCH in blood of full-term infants from birth to 76 days.

rose rather sharply, obviously because of more cells entering the circulation. After 90 days the average values for MCV, MCHC, and MCH, however, all continued to decrease as an increasing number of the infants were developing the characteristic blood picture of iron-deficiency anemia.

Variability observed in the second year arises from causes quite different from those discussed above. This is the period during which different degrees of iron-deficiency anemia may develop and recovery may occur after varying periods of time even in the absence of specific therapy. During these months our sample included infants with all degrees of iron deficiency as well as infants whose blood values closely approximated those of the average normal adult. This was demonstrated graphically by the histograms employed in two of the earlier reports [2,3] to illustrate the frequency distributions of the several blood values at different ages. The histograms suggest distinct bimodalism for values found within the group during the second year, especially apparent in the distributions of values for size and hemoglobin content of the cells. At this time there is apt to be wide variability in all characteristics of the red cells in many of the blood samples as well as wide variability between individual infants within the groups. In the absence of comprehensive studies of cell diameters we have no measurement of variability in the characteristics of the red cells that make up a cell population within individual samples of blood.

TABLE 9.—*Data on 167 Samples of Blood of Prematurely Born Infants and Infants of Twin or Triplet Birth*

Age Span in Days	No. of Cases	Red Blood Cells						Hemoglobin					
		Volume per Cent		Count, M/Cu. Mm.		MCV, Cubic Microns		In Whole Blood Gm. per 100 Cc.		In cells, MCHC, Gm. per 100 Cc.		Per Cell, MCH, $\gamma\gamma$	
		Mean± SE_m	±SE_σ	Mean± SE_m	±SE_σ	Mean± SE_m	±SE_σ	Mean± SE_m	±SE_σ	Mean± SE_m	±SE_σ	Mean± SE_m	±SE_σ
Cord Blood	15	52.9±1.1	4.1±0.8	4.622±0.117	0.455±0.083	117±1.9	7.2±1.3	17.5±0.4	1.6±0.3	32.5±0.4	1.6±0.3	37.9±0.5	2.0±0.4
1–9	12	56.3±1.8	6.3±1.3	5.168±0.164	0.567±0.116	109±2.8	9.8±2.0	18.7±0.6	2.1±0.4	33.3±0.4	1.2±0.3	36.2±0.8	2.7±0.5
10–29	20	46.7±2.3	10.4±1.6	4.621±0.190	0.852±0.135	105±1.5	6.7±1.1	16.4±0.7	3.3±0.5	33.8±0.4	1.7±0.3	35.5±0.5	2.4±0.4
30–90	33	43.1±1.5	8.8±1.1	3.485±0.156	0.898±0.111	95±1.3	7.7±0.9	11.2±0.5	3.0±0.4	34.0±0.2	1.4±0.2	32.2±0.5	3.1±0.4
91–151	9	31.0±1.4	4.3±1.0	3.573±0.238	0.715±0.169	88±2.9	8.5±2.1	10.1±0.5	1.5±0.4	32.8±0.3	1.0±0.2	28.7±0.9	2.6±0.6
152–212	6	32.2±2.1	5.1±1.5	4.307±0.278	0.681±0.196	76±5.6	13.8±4.0	10.3±1.0	2.4±0.7	31.7±1.1	2.0±0.8	24.3±0.8	1.9±0.5
213–273	17	30.4±0.7	3.1±0.5	4.804±0.145	0.596±0.103	63±1.8	7.3±1.2	8.7±0.3	1.3±0.2	28.3±0.5	2.1±0.4	18.0±0.8	3.1±0.5
274–334	11	28.5±1.7	5.6±1.2	4.942±0.286	0.817±0.174	59±2.2	7.4±1.6	7.7±0.6	2.0±0.4	26.8±0.7	2.3±0.5	15.6±0.9	3.1±0.7
335–394	9	28.4±1.0	3.0±0.7	5.092±0.211	0.632±0.149	56±1.8	5.5±1.3	7.7±0.4	1.2±0.3	27.0±1.0	3.0±0.7	15.3±1.0	2.9±0.6
395–821	35	30.6±0.9	5.4±0.6	4.795±0.106	0.639±0.076	64±1.5	8.9±1.1	8.9±0.4	2.3±0.3	28.8±0.2	1.1±0.1	18.5±0.8	4.6±0.6

In general it may be said that in the neonatal period variability in blood values may be ascribed mostly to physiologic adjustments to extrauterine life and in the second year mostly to nutritional differences between individual infants, especially in their iron stores. The variability at different periods is demonstrated numerically in the frequency distribution tables and graphically in the scatter charts; it is reflected also in the elevated values for standard deviations and standard errors common to all the figures in the neonatal period and in the second year.

Birth Order and Iron-Deficiency Anemia.—Early in the course of these studies we observed that in some families the successive siblings of infants in whom iron-deficiency anemia had been recognized showed tendencies to develop anemia at earlier ages and to a severer degree than the preceding siblings.[4,5] A plausible explanation then offered was that the successive siblings suffered increasingly severe iron deficiency because the mother's iron stores were depleted by successive pregnancies. If so, then it appeared likely that, in general, the first-born infants would be least prone to develop anemia.

Such tendencies were relatively easy to demonstrate within a few individual families when serial studies were done on successive infants followed from birth. When dealing with the general child population, in contrast to the families, scrutiny of individual case histories revealed a situation more difficult for statistical interpretation. Successive siblings of children known to be anemic or to have had anemia were frequently lost to our series because they received some form of iron as prophylaxis, sometimes before a laboratory diagnosis of even mild anemia could be made. This made it more difficult to be sure that the samples would be unbiased. Because later siblings in the family groups were frequently eliminated from the series, our whole group necessarily contained fewer later-born anemic infants than would be expected. Nevertheless, analysis of the total series did yield statistical evi-

TABLE 10.—*Packed Cell Volume (Hematocrit); Frequency Distributions at Different Ages—Infants of Premature or Twin or Triplet Birth*

Per Cent	Cord Blood	Age Span in Days								
		1–9	10–29	30–90	91–151	152–212	213–273	274–334	335–394	395–821
70–71.9		1								
68–69.9										
66–67.9										
64–65.9		1	1							
62–63.9			2							
60–61.9	1		1							
58–59.9	4	1	1							
56–57.9	1	2	2							
54–55.9	1	3								
52–53.9	4	2		1						
50–51.9	2	1	3							
48–49.9	1	1	1	1						
46–47.9	1		1	1						
44–45.9				2						
42–43.9			2	1						
40–41.9			4	2	1					
38–39.9						1				2
36–37.9				3		1		2		4
34–35.9				3		1	3			3
32–33.9				4	3	1	3		3	6
30–31.9			2	5	2		5	3		8
28–29.9				2	2		3	1	2	7
26–27.9				2	1	2	2	4	3	
24–25.9				3					1	1
22–23.9							1			2
20–21.9				1						
18–19.9				1						
16–17.9								1		1
14–15.9										1
12–13.9				1						
Total	15	12	20	33	9	6	17	11	9	35

dence supporting the hypothesis that had been based on observations on individual families.

Analysis of the influence of birth order was confined to children within the age span most critical for the development of iron-deficiency anemia. The data analyzed were from 461 samples of blood from children between 3 months and 1½ years of age and 790 samples of blood from children between 3 months and 3½ years of age. The numbers of samples from children in each age group, with position in the family, are listed in Table 16.

For evaluating differences between the different groups of siblings four indices of anemia were chosen: hemoglobin in whole blood, mean corpuscular volume, mean corpuscular hemoglobin concentration, and mean corpuscular hemoglobin. Analysis of

TABLE 11.—*Red Blood Cell Counts; Frequency Distributions at Different Ages—Infants of Premature or Twin or Triplet Birth*

Millions per Cu. Mm.	Cord Blood	Age Span in Days								
		1–9	10–29	30–90	91–151	152–212	213–273	274–334	335–394	395–821
6.2–6.39			1						1	1
6.0–6.19										
5.8–5.99		1							1	
5.6–5.79		2	3				1	1		
5.4–5.59	1	2	1				3	3		3
5.2–5.39		2		1			1	1		3
5.0–5.19	2	2	1		1	2	2	1	2	7
4.8–4.99	4	1	2	1			4	3	3	5
4.6–4.79			2	1			3	1	1	7
4.4–4.59	2		1	5						3
4.2–4.39	4		2	1	1	1				1
4.0–4.19	1	2	3	2			1		1	2
3.8–3.99	1		1			1				1
3.6–3.79			1	2	2	2	2			
3.4–3.59				2						
3.2–3.39			1	8	1					
3.0–3.19					2					1
2.8–2.99			1	4	2					1
2.6–2.79				1				1		
2.4–2.59				2						
2.2–2.39										
2.0–2.19				1						
1.8–1.99				1						
1.6–1.79										
1.4–1.59				1						
Total	15	12	20	33	9	6	17	11	9	35

TABLE 12.—*Mean Corpuscular Volume (MCV); Frequency Distributions at Different Ages—Infants of Premature or Twin or Triplet Birth*

Cubic Microns	Cord Blood	Age Span in Days								
		1-9	10-29	30-90	91-151	152-212	213-273	274-334	335-394	395-821
134-137.9	1									
130-133.9										
126-129.9	1	1								
122-125.9	1	1								
118-121.9	4	1								
114-117.9	4	1	3							
110-113.9	3		2	1						
106-109.9		2	3	2						
102-105.9	1	4	7	3						
98-101.9		2		5	2					
94-97.9				9	1					
90-93.9			2	4	1	2				
86-89.9				4	1					1
82-85.9				5	2					2
78-81.9					2	1	1			4
74-77.9						1	4	1		3
70-73.9							3	1		3
66-69.9						1	2		2	3
62-65.9						1	2	2	1	9
58-61.9							3	4	3	7
54-57.9							2	2	2	3
50-53.9								1	1	
46-49.9										
Total	15	12	20	33	9	6	17	11	9	35

TABLE 13.—*Hemoglobin in Whole Blood; Frequency Distributions at Different Ages—Infants of Premature or Twin or Triplet Birth*

Grams per 100 Cc.	Cord Blood	Age Span in Days								
		1-9	10-29	30-90	91-151	152-212	213-273	274-334	335-394	395-821
23-23.9		1								
22-22.9										
21-21.9		1	1							
20-20.9	1		2							
19-19.9	1	2	3							
18-18.9	3	4	1							
17-17.9	3	2	2	2						
16-16.9	6	1	2	1						
15-15.9	1	1	1	1						
14-14.9			3	1						
13-13.9			2	2	1					
12-12.9			1	5		2				5
11-11.9			1	4		1				2
10-10.9			1	7	3	1	3	2		4
9-9.9				4	4		3	1	2	6
8-8.9				3	1		5	2	2	7
7-7.9						2	5	3	2	4
6-6.9				2			1	2	3	3
5-5.9										2
4-4.9								1		2
3-3.9				1						
Total	15	12	20	33	9	6	17	11	9	35

TABLE 14.—*Mean Corpuscular Hemoglobin Concentration (MCHC); Frequency Distributions at Different Ages—Infants of Premature and Twin or Triplet Birth*

Grams per 100 Cc.	Cord Blood	Age Span in Days								
		1-9	10-29	30-90	91-151	152-212	213-273	274-334	335-394	395-821
37-37.9				1						
36-36.9			2							1
35-35.9	1	1	4	5	1					2
34-34.9	2	2	4	12		1				1
33-33.9	1	4	5	10	1	2				1
32-32.9	6	3	2	3	6					4
31-31.9	2	2	1	1	1	1	1			6
30-30.9	2		2				4			2
29-29.9	1			1		1	2	4	4	4
28-28.9							4			5
27-27.9						1	1	2	1	2
26-26.9							3	1	1	1
25-25.9								2	1	1
24-24.9							2			2
23-23.9								2		3
22-22.9									1	
21-21.9										
Total	15	12	20	33	9	6	17	11	9	35

TABLE 15.—*Mean Corpuscular Hemoglobin (MCH); Frequency Distributions at Different Ages—Infants of Premature or Twin or Triplet Birth*

Micromicrograms	Cord Blood	Age Span in Days								
		1–9	10–29	30–90	91–151	152–212	213–273	274–334	335–394	395–821
40–41.9	3	1	1							
38–39.9	4	2	1							
36–37.9	6	2	8	4						
34–35.9	1	5	8	7						
32–33.9	1	2		6	1					
30–31.9			1	7	2	2				
28–29.9			1	7	3					1
26–27.9				1	1					2
24–25.9				1	2	1				2
22–23.9							1			3
20–21.9						2	6	1		4
18–19.9							1	2	2	4
16–17.9						1	4	1	2	7
14–15.9							4	4	2	7
12–13.9							1	2	2	2
10–11.9								1	1	3
Total	15	12	20	33	9	6	17	11	9	35

the data demonstrated that the first-born infants had higher average values for each of these indices than later-born infants. In each case the differences observed, although small, were of decided statistical significance. The differences were most pronounced when those infants between 3 months and 1½ years of age were considered, but the differences were also significant for children between 3 months and 3½ years of age. For both groups the probability that the observed differences were due to errors of random sampling was less than 1 in 1000 ($P<0.001$) for hemoglobin in whole blood, MCHC, and MCH. The difference for MCV was significant at about this same level for the smaller group and at 0.02 for the group between 3 months and 3½ years of age. Further analysis indicated that the differences were greatest between the first-born and infants whose birth order was fourth or later. The differences existed but to a slightly less significant degree between the successive groups, i. e., first-born compared with second-, second- compared with third-, third- compared with the fourth- and all later-born siblings. In Figure 10 smoothed curves present graphically the mean values found at different ages among first-born infants and later siblings. The curves show clearly the favored position of the first-born infants.

For comparing the incidence of iron-deficiency anemia in first-born infants with its incidence in later-born infants, we used the mean corpuscular volume, MCV, as an index of the deficiency state. The data were arbitrarily divided into three groups, in which values less than 70 cu.μ were assumed to indicate severe anemia, values from 70 to

TABLE 16.—*Birth Order Within Age Groups*

Position in Family	Midpoint of Age Groups (Mo.)														Total
	4	6	8	10	12	14	16	18	Total 18 Mo. & <	20	24	30	36	42	
1	8	28	30	22	10	25	20	19	191	19	35	26	20	22	313
2	16	12	15	12	15	16	15	12	113	9	27	19	10	10	188
3	12	8	7	7	4	5	7	6	56	8	13	10	12	6	105
4	3	3	4	6	5	7	5	4	37	5	9	8	7	5	71
5	4	3	4	6	5		2	4	28	1	4	4	3	2	42
6	6	4	1	1	2		1	6	21	3	6	5	4	2	41
7			1		1			1	3	1	3	1			8
8				1					1		1			1	3
9		2		1				1	4		2	1		1	8
10				1					1		3				4
11	1	1	1						3						3
12		1	1						2	1					3
13															
14															
15															
16	1								1						1
	71	62	64	57	51	53	50	53	461	47	103	74	56	49	790

TABLE 17.—*Incidence of Microcytosis in First-Born Infants Compared with Later-Born Infants*

MCV, Cubic Microns	461 Infants Ages 3 Mo. to 1½ Yr. Birth Order				790 Infants Ages 3 Mo. to 3½ Yr. Birth Order			
	First-Born		Later-Born		First-Born		Later-Born	
	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent
Less than 70—severe anemia	37	19.4	73	27.0	54	17.2	97	20.3
70 to 77.9—moderate anemia	60	31.4	100	37.0	92	29.4	183	38.4
78 or more—no anemia	94	49.2	97	36.0	167	53.4	197	41.3
Totals	191		270		313		477	
	χ-square=8.9, p=0.01				χ-square=11.3, $p<0.001$			

78 cu.μ indicated moderate anemia, and values 78 cu.μ or more indicated no anemia. A two by three contingency table (Table 17) was constructed on this basis, and expected values were calculated for the group of children at ages 3 months to 1½ years and the group at ages 3 months to 3½ years. In both groups there were fewer first-born and more later-born siblings among the infants classified as having moderate to severe anemia and more first-born and fewer later-born siblings in the normal group than would be expected. For the age group 3 months to 1½ years the value of χ-square was 8.9, indicating a probability of about 1 in 100 (P=0.01) that the difference between observation and expectation could be due to errors of random sampling; for the age group 3 months to 3½ years the value of χ-square was 11.3, with a value for P of less than 0.001.

The figures on incidence indicate that microcytosis occurred more frequently in later-born siblings than in the first-born. In the group of infants 3 months to 1¼ years of age, MCV values of less than 78 cu.μ occurred in 50.8% of first-born and in 64% of later-born infants; in the group from 3 months to 3½ years of age the respective percentages of MCV values less than 78 cu.μ were 46.8 and 58.7.

These findings are in accord with observations made on single families previously reported.[4,5] For the large group they are particularly impressive, inasmuch as many later-born siblings of known anemic children were automatically omitted from the series because they were treated with iron.

Comment

Students of nutrition constantly face questions as to what values found within observed ranges of measurements of various characteristics for a given group of individuals may be considered normal and what values may be considered optimal or most desirable. "Normal" may be well defined as average when observed values are distributed normally, in the mathematical sense, and variability is low; for example, birth weights of infants (Anderson et al.,[12] Figs. 1 and 2). In the case of body temperature the normal may represent an upper limit, below which physiologic variation may commonly occur. Again, normal may signify the desired or optimal value, for example, pH of the blood, which is a value normally maintained within extremely narrow limits of variability, in which case normal and optimal might be used as synonyms. In our group of premature infants at 8 months of age, the low values for hemoglobin in whole blood were distributed over a narrow range. The average value of 8.7 gm. per 100 cc. described the group well and could therefore be considered "normal" for an untreated group of premature infants of that age. It is obvious, however, that this is not an optimal figure in the physiologic sense, for any group of 8-month-old infants. Such considerations indicate that values designated as normal may be but are not necessarily optimal. Physiological and biochemical characteristics are influenced by many factors, endogenous and exogenous, which must be recognized and rigidly specified in interpreting data.

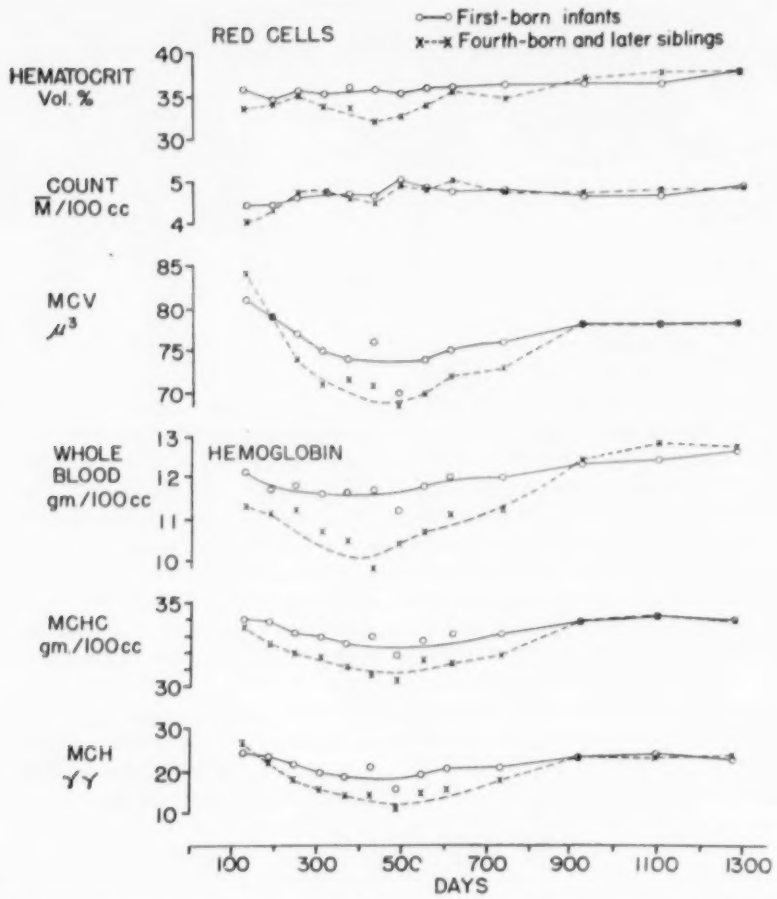

Fig. 10.—Curves represent averages of the several blood values among first-born and later-born infants.

We have used statistical methods extensively in describing the hematologic characteristics of the group of children studied. In interpreting the figures it is important to remember that even in a homogeneous population with values normally distributed, individual behavior cannot be prophesied by group behavior. For this group, at various times, the average values are almost certainly below the optimal levels. It should be borne in mind, however, that neither the mode nor the median would present a better or more accurate picture of the group.

It is apparent that average figures are higher for the more favored economic groups,[2] for the first-born compared with later-born siblings, and for full-term compared with prematurely born infants or infants of multiple birth. The observed differences in group behavior occurred, however, after the neonatal period. With our data it was impossible to demonstrate significant differences in any hematologic value during the first 3 months between full-term infants of single birth and the premature group or between first-born and the later-born infants. When mean values were plotted and joined by a smoothed curve the curves were found to be almost identical when superimposed upon each other as

shown in Figure 8. At 2½ to 3 months average values for all the direct measurements were low and average values for all the calculated indices closely approximated figures for the normal adult. From this time on, both group differences and individual differences began to appear; in some infants the hematocrit, red cell count, and hemoglobin values increased proportionately and all calculated indices remained at normal adult levels; in other infants mild microcytosis and hypochromia persisted for several months and then disappeared spontaneously; in still other infants microcytosis and hypochromia became progressively severer until iron therapy was begun. In every case, in our experience, ingestion of adequate amounts of iron resulted in prompt increases of all values to satisfactory levels, which were maintained after cessation of therapy.

It is noteworthy that in cases in which an abnormally high red cell count was associated with severe microcytosis and hypochromia, therapy resulted in a decrease in red cell count, while in those cases in which the red cell count was low, iron therapy was followed by increases in the red cell count. In a pair of twins with severe iron deficiency and extreme microcytosis and hypochromia, one twin had an initial red cell count of 2,980,000 while the sibling had a red cell count of 5,510,000. Both responded promptly to iron therapy, with rising values for hemoglobin in whole blood and for size and hemoglobin content of the cells. At the end of treatment both twins had red cell counts about 4,500,000 (Chart 3 in Guest, Brown, and Wing [2]).

Throughout this paper we have referred to even mild degrees of microcytosis and hypochromia of the red blood cells as indicating varying degrees of iron deficiency in the infants studied. This assumption is based on indirect evidence furnished in the past by many investigators, well reviewed by Wintrobe,[10] Josephs,[13] and others. The most important justification for this assumption is, we believe, the fact that in infants followed closely from birth, with blood samples examined at monthly intervals, the development of anemia could be predicted early, from curves depicting the pattern of changes in MCV, MCHC, and MCH, long before the level of hemoglobin in the whole blood fell significantly (Chart 2, Guest and Brown [1]). Another justification for the assumption is that in infants with low values for these indices the administration of iron provokes a prompt rise of the indices to levels that might be considered optimal. There is of course a possibility that deficiencies of other essential nutrients may play different roles which may influence the changes in size and hemoglobin content of the cells, either primarily or secondarily. However, it appears that deficiency of iron alone in most cases accounts adequately for the observed microcytosis and hypochromia, whether mild or severe.

In earlier papers dealing with various aspects of the studies summarized here we pointed out [5] that "the anemia of iron deficiency occurs among infants much more commonly than is generally recognized and far more often than it should in view of the abundant information now available on its nature and preventability." The observations cited in Table 1 suggest that in the 20 years or more since these studies were undertaken little has been done, at least in this typical community, about preventive treatment of iron-deficiency anemia in early childhood. The data show a high incidence of anemia (26% to 30%) among infants in the second year of life, both 20 years ago and now. The incidence undoubtedly would have been found even higher if only later-born infants had been considered in the tabulation. It is important to note that this type of anemia, mild or severe, often passes unrecognized during ordinary physical examinations and may be impossible to diagnose without laboratory tests. These observations point increasingly to the advisability of more widespread recommendations of iron supplementation in infant feeding and iron therapy to the mothers before and during successive pregnancies. The latter

phase of the problem merits thorough investigation.

The observations summarized in Tables 16 and 17 and in Figure 10 lead to an obvious conclusion that the tabulation of birth order of infants and interval between pregnancies should be included in group-survey studies of maternal and infant nutrition, especially when dealing with infants within the age span from 6 months to 3½ years.

Summary and Conclusions

This paper presents hematologic data on 1735 samples of blood, representative of a cross section of the white infant and child population of Cincinnati. Statistical methods were employed for the description of patterns of variability in hemoglobin levels in the blood and the number, size, and hemoglobin content of the erythrocytes at different ages.

Arithmetical means or averages are employed to indicate central tendencies in the age groups. Variability is indicated by figures for standard deviations and frequency distributions and portrayed graphically in scatter charts. Such statistical analysis necessitates the formulation of realistic concepts for the terms average, normal, and optimal. Values designated as normal or average may be, but are not necessarily, optimal.

During the neonatal period of about 80 days there were no significant differences in mean values between groups of full-term infants of single birth compared with premature infants and infants of multiple birth or between first-born compared with later-born infants. After the neonatal period differences between these groups are found increasingly, as varying degrees of microcytosis and hypochromia indicate the development of mild to severe degrees of iron deficiency through the third year and into the fourth. Group averages, especially during this period, do not represent optimal values.

Analysis of data on infants grouped according to birth order disclosed distinct differences between first-born and later-born infants. The first-born infants showed a significantly lower incidence of iron-deficiency anemia than the later-born infants, as indicated by the size and hemoglobin content of their erythrocytes, during the age-period most critical for the development of anemia.

At present the incidence of iron-deficiency anemia among infants in Cincinnati in the second year of age is about 30%, as high as was found when this study was done 20 years ago. These observations emphasize the need for more prophylactic iron therapy in early infancy.

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Sporadic Familial Goitrous Hypothyroidism

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Introduction

A survey of sporadic cretinism in the United States conducted by Sir William Osler in 1897 revealed that 7 among 60 cases studied were goitrous; moreover, 3 of those 7 cases were from one family of five children.[1] Observations with respect to sporadic goitrous hypothyroidism were not significantly enlarged upon until the introduction of I^{131} to clinical studies of human thyroid metabolism by Hamilton and Soley in 1939.[2] While sporadic goitrous hypothyroidism has subsequently undergone rather extensive investigation, attempts to clarify its pathophysiology are of recent origin.[3-16]

Eight children with this disorder are presented in this report in conjunction with data from laboratory investigations of their altered iodine metabolism. Pathologic data from these and other cases are described in a subsequent publication.[17]

Report of Cases

CASE 1.—A boy was born uneventfully on March 27, 1948, after a normal full-term pregnancy. The family had never resided in an area of endemic goiter, and there had been no known exposure to goitrogens. Early development was normal. Thyroid enlargement was first noted at 2 years of age. Thereafter the gland gradually increased in size. While physical growth slowed, other obvious signs or symptoms of hypothyroidism did not appear. At 5½ years he received a six weeks' course of thyroid extract (15 mg. [¼ gr.] per day) without evident effect.

He was first referred to the University of California Hospital* at the age of 6½ years. Signs of hypothyroidism, though present, were limited. Linear growth was stunted, and the bone age was retarded 2½ years. The thyroid was diffusely enlarged to three to four times normal size, and no nodules were palpable. A bruit was audible over the gland. His serum BEI† was 3.9γ per 100 cc.

The diagnosis of sporadic familial goitrous hypothyroidism was made, and the patient was placed on sodium *l*-thyroxine therapy (0.2 mg. per day). The goiter was barely palpable within a few weeks thereafter and a normal rate of body growth and bone maturation occurred, persisting through more than two years of follow-up and continued therapy. Serum BEI values have been maintained in the range of 7 to 10γ per 100 cc.

I^{131} studies were conducted before and during thyroxine therapy (at ages 6½ and 7½ years, respectively). On each occasion the effects of TSH administration on thyroid I^{131} uptake were investigated. Data from these studies are presented in conjunction with similar studies conducted on his sibling (Case 2) in Figure 1.

CASE 2.—A girl was born on Jan. 25, 1950, after a normal full-term pregnancy and uneventful delivery. She was the younger and only sibling of Case 1. Signs of hypothyroidism, including macroglossia, constipation, and growth and developmental retardation, developed insidiously in this child during the first year of age.

Thyroid enlargement was first noted at the age of 1½ years. Retarded development per-

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* Cases 1 through 7 were seen at the University of California Hospital. Case 8 was seen at the University of Oregon Hospital.

† Serum BEI: Serum butanol-extractable iodine was determined by the method of Man. Values in normal children range from 4.5 to 8γ per 100 cc.[18]

sisted and her thyroid continued to enlarge until the age of 2½ years. She then received 30 mg. (½ gr.) thyroid extract daily for six weeks. Her thyroid decreased in size, but when she was subsequently taken off therapy the thyroid again enlarged. She was admitted to this hospital for study at the age of 4½ years.

Examination revealed a short, stocky girl with multiple hypothyroid features and a retarded bone age of 2½ years. The thyroid was diffusely enlarged to three to four times normal size and was free of nodules. A bruit was audible over the gland. Her BEI was 2.5γ per 100 cc.

A thyroid I^{131} uptake study was consistent with the impression of sporadic familial goitrous hypothyroidism, and she was placed on sodium *l*-thyroxine (0.15 mg. to 0.2 mg. per day). She has subsequently remained on therapy for approximately three years. Serum BEI values have been maintained at or more than 7γ per 100 cc.

Coincident to the initial two to three weeks of thyroxine therapy, signs of hypothyroidism disappeared and growth and bone development became and have since remained normal. Her thyroid enlargement decreased rapidly, and the gland is now barely palpable.

I^{131} studies were conducted before the onset of thyroxine therapy (at age 4½ years) and again after one year of therapy. On each occasion the effect of exogenous TSH on I^{131} uptake by the thyroid was also studied.

Data from these studies are graphically presented, together with those of her brother, in Figure 1.

CASE 3.—A boy was born on Jan. 17, 1955, after a normal pregnancy and uneventful delivery. The parents had always resided in the San Francisco Bay region and enjoyed good health. There was no history of exposure to goitrogens. Two siblings, aged 2 years and 7 years, were in good health, without evidence of thyroid dysfunction.

The patient appeared well until the age of 2 months, when carotenosis became apparent. By the age of 3 months stridor became moderately prominent, and in the succeeding month appetite and weight gain were poor and growth was slowed. Thyroid enlargement became visible at the age of 4 months and increased at a rapid rate until his admission to this hospital 2 weeks later.

Examination on entry revealed evidence of thyroid deficiency, respiratory distress, and thyromegaly. No bruit could be detected over the area of thyroid. The gland was diffusely enlarged to three to four times normal size. His bone age was slightly retarded and body length was normal.

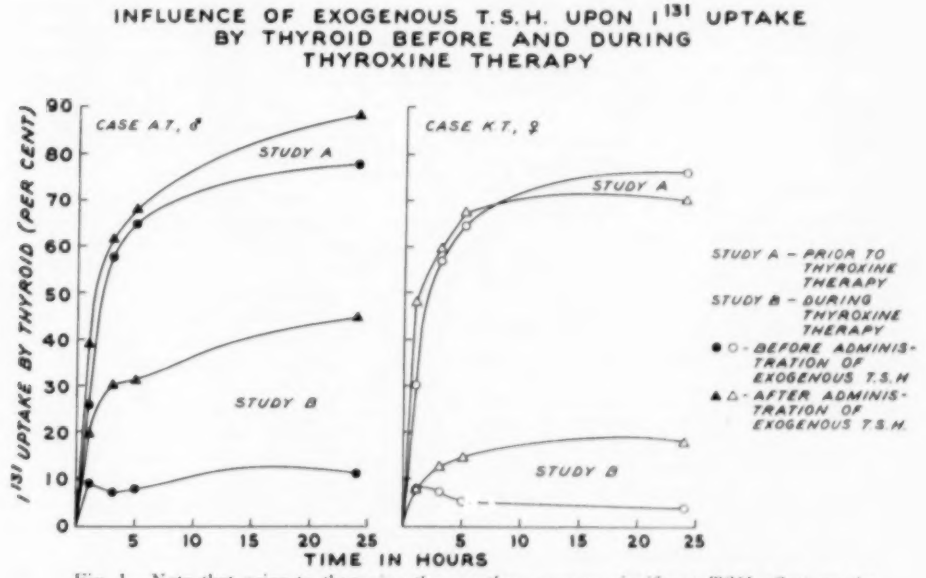
INFLUENCE OF EXOGENOUS T.S.H. UPON I 131 UPTAKE BY THYROID BEFORE AND DURING THYROXINE THERAPY
I 131 UPTAKE BY THYROID (PER CENT)
CASE A.T., ♂
STUDY A
STUDY B
CASE K.T., ♀
STUDY A
STUDY B
TIME IN HOURS
STUDY A – PRIOR TO THYROXINE THERAPY
STUDY B – DURING THYROXINE THERAPY
● ○ - BEFORE ADMINISTRATION OF EXOGENOUS T.S.H
▲ △ - AFTER ADMINISTRATION OF EXOGENOUS T.S.H.

Fig. 1.—Note that prior to thyroxine therapy there was no significant TSH effect on the markedly elevated I^{131} uptake, indicating that the thyroid gland was already responding maximally to endogenous TSH. During sodium *l*-thyroxine therapy there was suppression of I^{131} uptake and a significant response to exogenous TSH stimulation. (Case 1, at the left; Case 2, at the right.)

I^{131} studies revealed an accelerated I^{131} uptake by thyroid; uptake was 20% in one hour, 37% in three hours, and 44% in five hours.

Biopsy tissue of the thyroid isthmus showed an intense glandular hyperplasia.

The child was placed on treatment with sodium *l*-thyroxine (0.1 mg. per day). Dosage has been sufficient to maintain his serum BEI concentration at or slightly above the upper limits of normal. In response to therapy his thyroid enlargement and respiratory distress disappeared. At the age of 12 months his height and weight were normal, his IQ was 118, and his thyroid could not be palpated.

CASE 4.—A girl ‡ was born on Oct. 3, 1943, after an uneventful pregnancy and uncomplicated delivery. She has always resided in areas in which goiter is not endemic and has not been exposed to goitrogens.

Thyroid enlargement became evident at approximately 2 years of age and increased slowly thereafter.

She was first seen at this hospital at the age of 4½ years, at which time she was hypothyroid with moderate mental retardation. Her bone age was then retarded nearly 2 years. The thyroid was diffusely enlarged to three or four times normal size, and no bruit was audible. I^{131} uptake by thyroid was greater than normal. She received strong iodine (Lugol's) solution U. S. P. regularly during the next year; signs of hypothyroidism and goiter persisted. During the next five years she received 60 to 90 mg. (1 to 1½ gr.) of thyroid extract per day. During the first five months of such therapy her thyroid decreased to one and one-half times normal size and signs of thyroid deficiency disappeared almost completely. Between the ages of 9½ and 10 years she was treated with sodium *l*-thyroxine in relatively larger doses (0.15 to 0.2 mg. per day). Thereafter she received 0.3 mg. daily, a dosage which elevated her serum BEI to more than 7γ per 100 cc. The gland became of normal size, and growth and bone age likewise became normal. When last seen, at the age of 11 years, the thyroid was not palpably enlarged. Her I. Q. was approximately 70.

I^{131} uptake studies were conducted at the age of 9½ years (before thyroxine therapy) and again at 10½ years, after one year of such therapy. On each occasion she had been off all therapy for a two-week period. Effects of exogenous TSH on uptake were analyzed in the study at 9½ years. Data from I^{131} studies are presented in the Table.

I^{131} Uptake by Thyroid in Case 4

Hours Following I^{131} Administration	I^{131} Uptake (%) by Thyroid at Age			
	4½ Yr.	9½ Yr.		10½ Yr.
		(Pre-TSH	(Post-TSH)	
1		9.4	12.3	27
3	70	28.1	40.7	47
5		36.3	63.6	56
24	42	69.8	85	65

CASE 5.—A boy was born at term on April 29, 1940, after an uneventful pregnancy and delivery. He has always resided in a goiter-free area and has not been exposed to goitrogens. He has no siblings.

This patient was first seen at this hospital at the age of 2½ months, at which time classical signs and symptoms of cretinism were present. He had a deep cry, dry skin with peripheral mottling, hypothermia, constipation, umbilical hernia, and macroglossia. Weight gain and growth had been poor during the preceding two months. The thyroid was not palpable. During the ensuing 11 years he was given 60 to 120 mg. (1 to 2 gr.) of dessicated thyroid a day, a dosage insufficient to completely correct his hypothyroidism.[20,21]

He was readmitted to this hospital at the age of 11 years 6 months for evaluation of thyroid enlargement which had become apparent 4 months earlier and which had thereafter increased rapidly. The gland was approximately three to four times normal size, firm, and somewhat nodular. A bruit was not detected. His bone age was retarded 2 years and epiphyseal dysgenesis was present. His I. Q. was approximately 70.

After two weeks off therapy his BEI was 2.8γ per 100 cc. Thyroid I^{131} uptake was rapid, with an early plateau at 78% by 5 hours and a significant loss of I^{131} (25%) through the remainder of the initial 24 hours of study. A subtotal thyroidectomy was performed. Histologically the thyroid tissue showed areas of atypical atrophy and adenomas of multiple variety.

Therapy was reinstituted with sodium *l*-thyroxine (0.3 mg. per day). When last seen, at 14½ years, the patient was doing well. Bone growth and maturation had become and remained normal, and epiphyseal dysgenesis had disappeared. His BEI ranged from 7 to 9γ per 100 cc. The goiter has not recurred.

CASE 6.—A girl was born on Dec. 21, 1955, after an uneventful pregnancy and normal delivery. Both parents are euthyroid and have resided in San Francisco only.

‡ An older sibling developed hypothyroidism with goiter approximately five years earlier than this child and clinically in much the same sequence. That child was reported by Hamilton et al. in 1943.[5]

Difficult and slow feeding, progressive inactivity and lethargy, a protruding large tongue, a small umbilical hernia, poor weight gain, and an increasingly hoarse cry had developed during the first month of life. At the age of 5 weeks she was admitted to the hospital with classical signs of cretinism: Examination revealed lethargy, puffy eyelids, a large protruding tongue, a small umbilical hernia, and generalized skin mottling. The thyroid was not palpable.

Her serum BEI was 1.0γ per 100 cc.; I^{131} uptake by thyroid was 13% in one hour, 13% in three hours, 11% in five hours, and 3% in twenty-four hours.

A skeletal survey showed a normal bone age. Psychometric testing revealed a probably normal development.

Treatment with sodium *l*-thyroxine (0.1 mg. daily) was started at the age of 6 weeks. During the first week of therapy there was noticeable improvement in her activity, feeding, and general appearance. During the ensuing nine months all aspects of development and growth have been normal. The thyroid gland has remained nonpalpable.

CASE 7.—A girl was born on Aug. 30, 1948, after a normal full-term pregnancy and uneventful delivery. She has always resided in a goiter-free area and has not been exposed to known goitrogens. Her parents and two siblings are living and well without thyroid dysfunction or goiter.

Her development during infancy and early childhood was normal. Small enlargements of the upper poles of the thyroid, however, were noted soon after birth. They persisted without change. During her 4th year of life she gradually developed moderate listlessness, her voice deepened, and constipation became a problem. These signs persisted and were gradually accompanied by carotenosis and slowed growth. At the age of 5¼ years a generalized enlargement of the thyroid became apparent. This increased rapidly during the ensuing six months.

She was admitted to the hospital at the age of 6 years. Examination confirmed her hypothyroid status. Her thyroid was enlarged to three to four times normal size and was nodular. I^{131} uptake by the thyroid was 62% at the end of 24 hours. Repeat uptake studies and an I^{131} scintigram (48 hours) again demonstrated the exaggerated uptake and showed that I^{131} was distributed generally throughout the gland except for the nodules, in which no activity could be detected (Fig. 2).

Because of tracheal compression and the possibility that the nodules might represent carcinoma, a subtotal thyroidectomy was performed. Pathologic examination showed goitrous tissue comprised of small colloid-free follicles lined by large, pleomorphic cells and adenomas of various types. After surgery she was placed on thyroid therapy and has since shown no signs of hypothyroidism or recurrent goiter.

CASE 8.—A boy was born at term after a normal pregnancy and an uncomplicated delivery. The

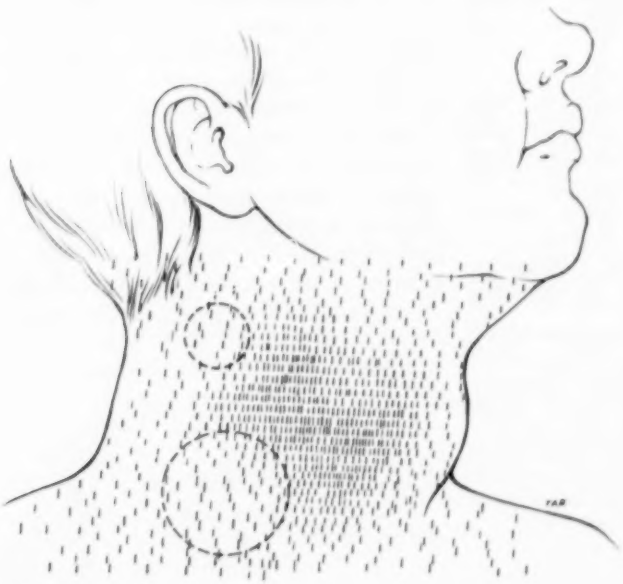

Fig. 2.—Note that I^{131} was distributed uniformly throughout the goiter with the exception of the nodules (indicated by broken circles).

family has always resided in a goiter-free area, and there has been no history of exposure to goitrogens. The child's father and mother have no history of thyroid dysfunction or goiter. One young sibling is well.

Growth and development were apparently normal until 3 years of age, when goiter appeared. During the ensuing six months this goiter increased in size. He then developed difficulty in swallowing over a period of one to two weeks.

When admitted to the hospital for study his bone age was retarded 1½ years. Serum hormonal iodine (PBI)§ was 3.75γ per 100 cc. This was taken to represent a normal value; however, it is obviously consistent with hypothyroidism. The 24-hour I^{131} uptake by thyroid was 71%. By 72 hours only 47% of the initial dose remained in the gland. The right lobe of his thyroid, including parathyroids and the isthmus was removed surgically. The pathologic specimen showed a near-absence of colloid and evidence of a typical glandular hyperplasia.

On the third postoperative month thyromegaly recurred, and it gradually increased during the ensuing six weeks. He came to the attention of one of us four and one-half months following surgery. He was then hypothyroid and his thyroid was palpably enlarged, the left lobe being one and a half to two times normal size. He was subsequently treated as a sporadic familial goitrous hypothyroid child for a period of 10 months with sodium *l*-thyroxine (0.25 to 0.3 mg. daily). Thyromegaly and signs of hypothyroidism disappeared. Growth and bone development are now normal. Serum BEI concentration has been maintained at approximately 7γ per 100 cc.

Comment

Heredity ‖.—Sporadic goitrous hypothyroidism occurs only 5% to 10% as frequently as sporadic nongoitrous cretinism. It is further contrasted from the latter by a high rate of incidence among related siblings.[1,10,12,23-27] Among children presented in this communication, sibling involvement occurred in three out of eight chances, in keeping with over-all reported statistics which show that approximately one-half of siblings are afflicted and also in keeping with the opinion that this condition is an inborn error of metabolism probably transmitted by a recessive autosomal gene.[1,4,5,7-12,28]

Clinical Variation.—Though evidence of goiter may antedate signs of hypothyroidism (and vice versa) and though the relative severity of the two need not be parallel, relationships of these features of the disorder have tended to be uniform among cases appearing in any one family in the present report and in other reports.[1,4,10,11,28,29]

Variation in the degree of hypothyroidism among cases would logically relate directly to variation in the quantitative and qualitative aspects of thyroxine production and release. Hypothyroidism may be severe and apparent in early infancy. On the other hand, it may not be manifest until the second or as late as the third decade and then may be of minimal severity. Signs and symptoms and the ultimate development of irreversible stigmata of the disorder (mental retardation) relate directly to the age of onset, the degree of the deficiency, and the time lapse between the onset of deficiency and institution of adequate therapy, as is true in the nongoitrous sporadic hypothyroid infant or child.[29,30]

The age at which the goiter appears and its morphologic structure depend on the degree of thyroid deficiency and the potentiality of the gland for a sustained hyperplasia secondary to increased quantities of pituitary TSH (released by the pituitary in response to the thyroxine deficiency). At any time, the size of the gland and its histologic characteristics are dependent upon synthesis of these many factors.[17]

It is logical that hypothyroidism would appear very early in association with a rapidly growing diffuse goiter when the error in hormone synthesis is near-complete and the gland is comprised of a sufficient bulk of responsive tissue. Such a situation

§ Serum protein-bound iodine was determined by a modification of the method of Barker.[22]

‖ In passing, it seems appropriate to contrast this condition with endemic cretinism as far as heredity is concerned. In geographic areas where there is a 45% to 50% incidence of endemic goiter, 55% of cretins are goitrous and in nearly all instances their mothers are goitrous as well. Despite this, a genetic predisposition to endemic cretinism with or without goiter has been clearly ruled out.[31]

was observed in Cases 1-4. On the other hand, goiter would not be expected until late in children with an equally severe deficiency of hormone synthesis and in whom there exists only rudimentary fragments of tissue capable of responding to the excess TSH stimulation. Case 5 is representative. He was a classical sporadic cretin without apparent goiter in early infancy. After more than nine years of therapy inadequate in terms of pituitary suppression, he finally developed goiter.

Goiter should not appear under conditions of adequate therapy, instituted and sustained from infancy. Case 6 probably exemplifies this point; she developed severe hypothyroidism without goiter at the age of 3 weeks. I^{131} uptake studies showed the presence of potentially goitrous thyroid tissue. Adequate therapy maintained from early infancy in her case has, in addition to the more essential job of providing normal growth and development, presumably prevented development of a goiter.

In some instances initial deficiency of hormone synthesis by the thyroid may be less severe. Under such circumstances hypothyroidism might appear in later childhood and usually follows the appearance of a goiter. Cases 7 and 8 are representative.

Iodine Metabolism.—The essential abnormalities of iodine metabolism in sporadic familial goitrous hypothyroidism are most clearly envisioned when the central defect in hormone synthesis and related secondary events are likened to the well-established series of changes which follow use of goitrogens, such as thiourea and derivatives.[32,40]

These children appear to have normal iodide-trapping mechanisms in the thyroid; moreover, this function can respond to excess TSH by an accelerated iodide uptake.[3,11,16] This is to be contrasted to the much reduced and often absent iodide uptake observed in nongoitrous cretins.[3,19,20,23]

The present studies present evidence supporting the hypothesis that the increased I^{131} uptake and a significant proportion (initially, probably all) of thyroid enlargement is secondary to TSH excess.[16,17] Administration of sodium *l*-thyroxine in quantities adequate to suppress pituitary TSH release (and I^{131} uptake) in normal subjects effected an equal suppression of I^{131} uptake and a rapid disappearance of goiters in Cases 1-4, and 8. I^{131} studies conducted during therapy in Cases 1 and 2 revealed a nearly complete inhibition of I^{131} uptake by thyroid. It is evident that this was due to thyroxine suppression of their pituitary TSH release, since under similar conditions of thyroxine administration I^{131} uptake was again increased to nearly normal levels following injection of small doses of TSH over a 48-hour period. An equal quantity of TSH administered before thyroxine inhibition had little or no effect on their I^{131} uptakes. It has been experimentally and clinically established that, whereas the injection of TSH has little or no significant effect on I^{131} uptake in the presence of normal amounts of endogenous TSH, a similar amount administered during TSH suppression is attended by a significant increase in I^{131} uptake.[16,19,34-36]

The increased uptake induced by small amounts of TSH in Cases 1 and 2 after one year of pituitary suppression shows that thyroxine therapy is not likely to lead to atrophy of the gland and that treatment must be maintained indefinitely. This is also suggested by the observations in Case 4 that there occurs a rapid return of I^{131} uptake after two weeks off treatment despite a previous long period of hormone administration.

Despite the integrity of the thyroid iodide-trapping mechanisms, sporadic goitrous hypothyroid children are unable to synthesize thyroxine adequately.[7,8,10,11,28,37] Some insight has been gained relative to the error in hormone synthesis. These children are variably able to synthesize the hormone precursors mono- and diiodotyrosine.[3,11] In instances in which this synthesis of mono- and diiodotyrosine is inadequate, there is an abnormally large release of trapped iodide following administration of potassium

thiocyanate, a procedure which displaces the thyroid iodide which has not entered the hormonal organic moiety.[5,6,40,41]

Evidence has recently been reported which indicates a pathological metabolism of mono- and diiodotyrosine by these patients. In contrast to normal persons, they do not effectively dehalogenate iodotyrosines, either in thyroid or in extrathyroid tissues.[13-15] In the thyroid gland this defect leads to the rapid appearance of those substances in plasma; moreover, lack of dehalogenation by extrathyroidal tissues results in their abnormal and rapid appearance in urine, and a normal recycling of iodide within the body is prevented.[13-15] ¶ Recycling of iodide by the thyroid and by the body as a whole is considered to be an essential phase in normal iodine metabolism. It is felt that, along with triiodothyronine and thyroxine, mono- and diiodotyrosine are mobilized in the process of hormone mobilization and that the latter substances are normally deiodinated before release by the gland and that they therefore do not reach the blood in any appreciable concentration.[38,39]

According to Harrington, the oxidation of iodide to hypoiodite is a fundamental and necessary step in hormone synthesis, not only with respect to the precursors mono- and diiodotyrosine but, more importantly, to final steps in thyroxine synthesis.[40] Could not the primary difficulty in hormone synthesis by these children's thyroids be a deficiency in the effective concentration of the oxidative enzyme(s) responsible for the oxidation of iodide and final precursor linkage? It is of interest that TSH stimulation in persons without this anomaly (e. g., in thyrotoxicosis) is associated with an increased rate of organification of iodide trapped by thyroid.[43] Of related significance is the observation that an increase in rat thyroid peroxidase occurs during TSH stimulation.[44]

Irrespective of the primary etiology, goitrous hypothyroidism is a severe inherited error of metabolism. Because it frequently occurs in early infancy and frequently escapes early detection (and the early introduction of adequate therapy), it is oftentimes associated with mental deficiency. Therapy must be singularly geared to providing thyroid hormone in amounts adequate to eradicate the hypothyroid state in its fullest implication. If treatment is adequate, the goiter, which is really of secondary importance, will abate. Such therapy must be sustained indefinitely.

The normal mental development demonstrated by the two infants (Cases 3 and 6) in whom diagnosis and adequate therapy with sodium *l*-throxine was introduced early is in marked contrast to the very common observation of mental deficiency in comparable cases in which adequate therapy is delayed, whether by virtue of late diagnosis or of administration of inadequate amounts of hormone.

It is clearly of clinical importance that establishment of the diagnosis of goitrous sporadic hypothyroidism in one child in a family carries with it the responsibility to examine siblings of that child for evidence of the disorder and to alert parents to the likelihood that subsequent offspring may be similarly involved.

Summary

Eight children with sporadic goitrous hypothyroidism, representative of particular problems in diagnosis and therapy of that disorder, are presented along with studies relating to their altered iodine metabolism and observations as to their response to treatment with sodium *l*-thyroxine.

Hypothyroidism and ultimately goiter are secondary to inadequate thyroxine synthesis by the thyroid gland. Treatment with sodium *l*-thyroxine results in an eradication of signs of hypothyroidism and goiter with the following exceptions: (*a*) mental re-

¶ Similarly, Costa et al. have observed zones corresponding to diiodotyrosine in chromatograms of sera from two patients with endemic cretinism who were given I^{131}. This is a particularly fascinating observation in light of differences in inheritence of these two disorders.[42]

tardation persists if thyroid deficiency has not been corrected during early infancy; (*b*) fibrosed thyroid nodules may remain despite adequate therapy.

A discussion pertaining to heredity, clinical variation, and possible faulty enzymic mechanisms responsible for the defect of hormone synthesis is also presented.

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Some Observations on 1246 Cases of Geographic Tongue

The Association Between Geographic Tongue, Seborrheic Dermatitis, and Spasmodic Bronchitis—Transition of Geographic Tongue to Fissured Tongue

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One of us (P. R.) had the opportunity of working in the city of Jaffa right after the establishment of the state of Israel. Our attention was called to the condition of geographic tongue by the frequency of this condition among the population of Jaffa. Over a period of five years (June, 1949-June, 1954) we observed 1246 children with geographic tongue out of a total number of 8305 examined, which amounts to 15%. Such a high percentage has never been described before.

Out of the total of children observed, 5425 were infants up to 2 years of age and 775 of them (14.29%) had geographic tongue.

The observations were made in the center of the city of Jaffa, which up to 1948 had been inhabited by Arabs. During the Arab-Israeli war the city was abandoned by the Arabs and afterward settled by Jews who had immigrated from Central, Eastern, and Southeastern Europe. The new inhabitants represented survivors from concentration camps coming mainly from Poland, Hungary, Czechoslovakia, Greece, Bulgaria, and a few from Turkey and other countries. Some families from Jerusalem were also transferred there, their homes having been destroyed during the war.

Most of the children included in the survey were born in Jaffa and only a few were born abroad. A large number of cases were observed continuously, some for a period of one-three years, others for several months only, depending on the time the families resided in Jaffa, since for some of these new settlers Jaffa was just a transit camp before moving elsewhere. Since some of the children were born abroad, we were already acquainted with the disease as it occurred in Europe.

For the purpose of this paper we selected out of our records only the data on children up to 2 years—5425 children—among them 775 cases of geographic tongue. This enables us to emphasize clearly the connection existing between geographic tongue and other conditions prevailing at this age, such as seborrheic dermatitis and spasmodic bronchitis.

To substantiate the other finding—transition from geographic tongue to fissured tongue—we used all the data, i. e., 8305 children, among them 1246 cases of geographic tongue, thus including children above the age of 2 as well. Some of these cases were followed up for longer periods, five to eight years and sometimes even more than eight years.

Definition

Geographic tongue * is defined as follows:

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* Synonyms: *état lichenoïde* (Gübler, 1869), *état tigré de la langue* (Bridon, 1872), *exfoliatione areata della lingua* (Mibelli, 1880), *psoriasis der Zungenschleimhaut* (Kaposi, 1873), *glossite exfoliatrice marginée* (Lermonier, 1883), *transitory benign plaques of the tongue* (Hertzell, 1887), *wandering rash* (1880), *eczema en aires de la langue* (Bernier, 1889), *Landkartenzunge, Möllersche glossitis superficialis* (Spehlman, 1892).[1]

We first recognize this clinical entity by the small, round, grayish areas which appear on the dorsum and rapidly enlarge, extending to the middle of the tongue. The advancing margin is somewhat elevated and gray, while the desquamating center presents a reddened surface. The various areas on coalescing produce the typical maplike appearance (Jay Durand[3]).

Fissured tongue (furrowed tongue, scrotal tongue), on the other hand, is a tongue crossed by many deep grooves in a regular or irregular pattern. The pattern may be foliaceous (leaf-like) or cerebriform (Nelson[3]).

Geographic tongue was first described by Rayer in 1831 under the name of "Pityriasis of the Tongue." Since then this condition has been described under different names and varying importance has been attributed to it. Some believed that it was caused by fungi, bacteria, syphilis, etc. Others ascribed it to avitaminosis. Czerny regarded it as a sign of diathesis exudativa.

The etiology and importance of this condition remain obscure. Most textbooks mention geographic tongue very briefly, stating that no treatment is required, since it seems to cause no subjective complaints.

Association with Other Diseases

Seborrheic Dermatitis.—This disease is most commonly seen in young infants. The specific skin changes consist of red scaly papillae and scaly plaques of psoriatic appearance. In addition, there are areas of fatty crusts, on the head mainly, then on the face, and more rarely on the trunk and limbs. As background for both, there is the dry, more or less spreading erythrodermia that may, under the influence of maceration, become inflamed, swollen, and wet.

These foci, when present, are not the disease but its symptoms. They do not represent eruptions but specific sickly reactions of a general defectively constituted skin to common outside stimuli that do not seem to harm the normal skin. In short it consists of a seborrheic state of reactions of the skin.

P. György believes it to be caused by a combination of two factors: A toxic action from the absorption of unsplit lactalbumin and deficiency of a vitamin which he calls vitamin "H"—*Hautfaktor* (*Haut*=skin). This vitamin in milk is associated with casein and is more abundant in bovine than in human milk. Hence the benefit of adding casein to the diet of infants with seborrheic dermatitis.[2,5]

Of the three conditions—seborrheic dermatitis, spasmodic bronchitis, and geographic tongue—seborrheic dermatitis almost always appears first. It also appears approximately at the same tender age in cases which subsequently fail to develop the other conditions.

Out of the 775 cases of geographic tongue, 133 (17.1%) developed seborrheic dermatitis. Of the total number of 4650 there were 185 found to have seborrheic dermatitis without the appearance of geographic tongue (4%).

Appearance of seborrheic dermatitis in children up to 2 years was as follows:

1 week to 6 months	92 cases
7 months to 12 months	30 cases
12 months to 24 months	11 cases
Total	133 cases

Association coefficient for seborrheic dermatitis—0.60.

By association between a disease and geographic tongue we refer to the fact that the disease is relatively more frequent among patients with geographic tongue than in other infants, irrespective of the absolute or relative frequency of the diseases.

Estimation of the degree of association is done according to Yule's coefficient of association. This coefficient becomes zero in the absence of association, i. e., when the disease occurs as often (relatively) in children with geographic tongue as in children without it. It assumes the value 1 in the case of complete association, i. e., that

either all cases of geographic tongue have this other disease too or that not a single case without geographic tongue has the other disease. According to this definition, a coefficient of association with a value of 0.6 is considered very high.

Spasmodic Bronchitis.—Many infants who have no personal or family history of allergy have a tendency toward spasmodic bronchitis in association with acute respiratory infections. There is a certain amount of respiratory distress, and wheezing and musical rales are present on auscultation. There is no eosinophilia and no relief from epinephrine. In some children this tendency is so marked as to suggest a peculiar constitutional type of reaction. As the child grows older, this tendency to have spasmodic bronchitis disappears. During the first such attack it is not always possible to determine whether allergic asthma is a factor. The presence of a positive personal or familial history of allergy, of eosinophilia and response to epinephrine strongly suggests an allergic basis for the attack.[3]

Finkelstein adds to the above-mentioned differential diagnosis the fact that spasmodic bronchitis appears at a more tender age, while asthma appears at a later period. Besides the spasmodic bronchitis there are changes in the skin of the kind of seborrheic dermatitis, changes in which there is no increased eosinophilia, while in asthma the changes in skin are of the true eczema type (atopic eczema) and there is increased eosinophilia. The prognosis of spasmodic bronchitis is good, and the pathologic phenomena disappear after several repetitions of the disease.[4]

Out of the 775 cases with geographic tongue spasmodic bronchitis appeared in 124 cases (16%), while in the 4650 children without geographic tongue there were 259 cases (5.6%).

Time of onset was as follows:

1 week to 6 months	46 cases
7 months to 12 months	43 cases
12 months to 24 months	35 cases
Total	124 cases

While seborrheic dermatitis appears mainly during the first half year of the child's life, the onset of spasmodic bronchitis is equally frequent in the first and second halves of the first year. It decreases in the second year, but the decline is not

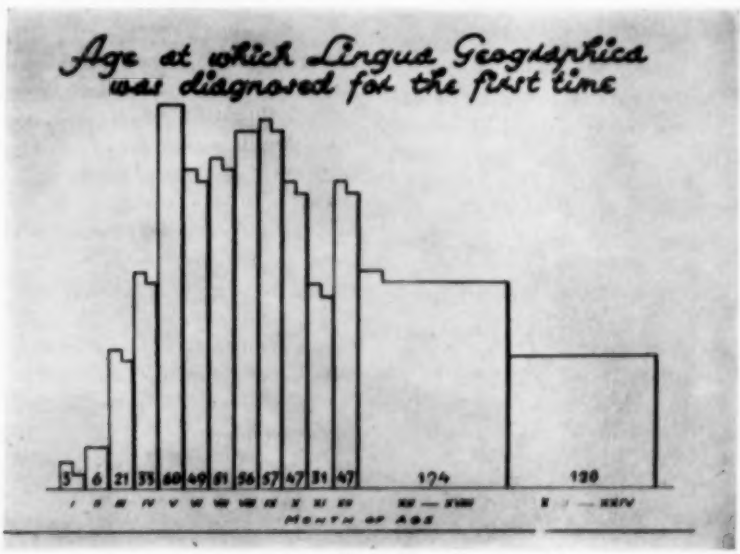

Figure 1

Association of Seborrheic Dermatitis, Spasmodic Bronchitis, and Geographic Tongue

Dermatitis Seborrhoid	Bronchitis Spastica	Lingua Geographica	No. of Cases
+	−	+	94
−	+	+	85
+	+	+	39
+	+	−	15

very sharp. The association coefficient is 0.53.

Geographic tongue appears at the same age seborrheic dermatitis and spasmodic bronchitis do.

Mean Age of First Onset of Geographic Tongue.—In estimating the age at which the first onset of a certain disease or condition occurs, it must be taken into consideration that a patient might have suffered from the disease or condition before consulting a physician and that the disease or condition might not have been diagnosed at the first visit. Both factors have the tendency to raise the estimated age of first onset of the disease.

From Figure 1 it can be seen that seldom is it possible to diagnose geographic tongue in the child's first 3 months. After the third month the number of cases increases, and in the second half year it is at its highest.

Relationship of the Diseases

There are three states with a chronologic order in the onset of the three diseases, seborrheic dermatitis, spasmodic bronchitis, and geographic tongue. First seborrheic dermatitis appears, then spasmodic bronchitis, and then geographic tongue. This way they form an age syndrome, a triad, which occurs in a greater frequency in comparison with other associations encountered at an older age.

The Table demonstrates the size of association between these three conditions in the frequency of their occurrence.

The total syndrome of the three conditions appeared in 39 cases. Taken absolutely this number is small, but relatively, i. e., as compared with the probability of the simultaneous occurrence of three rare conditions, this is quite a high frequency. It should furthermore be taken into consideration that we did not follow all the cases from birth till the age of 2. Thus, in children who came to us later we found only spasmodic bronchitis and geographic tongue, while seborrheic dermatitis which appears mainly in the first 3 months could not always be determined. Also, owing to irregular check-ups on all the diseases at a later age, it is very probable that in several cases we did not see the spasmodic bronchitis. Had all the children been examined regularly, the number of children with a full syndrome would certainly be larger. At the end of the first year and in the second year associations between geographic tongue and other diseases show up, but it should be stated right here that their association is much weaker than that observed in the above-mentioned group.

Other Associations

Anorexia.—Among 775 children with geographic tongue, anorexia was encountered in 267 cases (34.4%). In the control group of 4650 children there were 753 cases, or 16.1%. The association coefficient here is 0.47.

This coefficient of association is, in fact, also high, but too much importance should not be attached to this finding, since anorexia is a relatively frequent condition in the control group as well. Its importance is nevertheless considerable, and the association is highly significant from both the medical and statistical point of view.

Insomnia.—Out of all the 775 cases of geographic tongue, insomnia was found in 77 children only (9.9%), as compared with 214 cases in the control group (4.6%); association coefficient was 0.31.

Urticaria Papulosa Infantum—Strophulus.—Strophulus was found in 51 cases out of the 775 cases with geographic tongue (6.7%), while in the control group there were 123 cases (2.6%). Association coefficient was 0.43.

Respiratory Affect Cramps.—These appear sometimes at the end of the first year, but usually they appear later. For some reason, like fear, anger, deprivation of a toy, being forbidden to do something or getting refusal of a wish, the child begins to cry violently. In the middle of this crying he sometimes stops breathing for about a minute. He becomes cyanotic, especially around the lips and in the case, looks around him with fear, and waves his arms and legs helplessly. Frequently the eyes turn upward, and, here and there, it may come to flashlike convulsions.[6]

The total number of cases observed is quite small. Altogether there were 42, but 22 of them were among the group of 775 with geographic tongue and 20 in the control group. The association coefficient is very high, 0.74.

From all the observations it was noted that there was no difference between boys and girls regarding the appearance of geographic tongue. Out of 2886 boys 453 had geographic tongue (15.7%), and out of 2539 girls 322 had geographic tongue (12.69%), a slight dominance in boys.

No considerable differences were observed in connection with the seasons. This lack of connection to a certain season points against the possibility of avitaminosis being the cause of geographic tongue, since, in general, avitaminosis is encountered more frequently in certain seasons than in others. Against avitaminosis also points the fact that geographic tongue has been observed for years without any other sign of avitaminosis.

It should be mentioned here that in 417 children (53.8%) geographic tongue was discovered on the first examination, in 135 cases (17.4%) it was discovered on the second one, and in the other 223 cases (28.8%) only on the third one or later. Hence, in only up to 53.8% of the cases could geographic tongue be diagnosed on first examination, and additional examinations were required to diagnose the other 46.2%. Therefore, in order to determine the prevalence of geographic tongue in a certain group of children, they must be observed several times over a longer period.

Transition from Geographic Tongue to Fissured Tongue.—In 41 of the children with geographic tongue the transition to fissured tongue could be determined. This could obviously be done mainly in children who were under observation for an extensive period (three to five years). Some who were on file from Europe could be followed for more than 8 years and one case even for 17 years.

Another outstanding fact from these observations is that a large number of parents of children with geographic tongue were found to have fissured tongue, and only a small percentage of the parents had geographic tongue. Out of 373 parents of children with geographic tongue examined, 140 had fissured tongue (38%) and 29 had geographic tongue (7%). This can be considered as a direct indication for the transition of geographic tongue to fissured tongue and as strong evidence for transmission through inheritance.

A third fact worth noticing is that in eight children with geographic tongue born between 1943 and 1948 and followed through 1953 we could determine the simultaneous presence of geographic tongue in certain parts of the tongue and fissured tongue in other parts. The coexistence of geographic tongue and fissured tongue, as well as the transition from the first to the second, prove that in a certain proportion of cases fissured tongue is only a later state. An isolated case of this type has been described in the literature as early as 1903, "A Case of Scrotal Tongue with Wandering Rash."[7]

R. Turpin and A. Caratzali state that "*La Glossite Exfoliatrice Marginée*" (geographic tongue) is much more prevalent in first and second childhood periods. When children with geographic tongue are observed during a continuous period, it can be noted that geographic tongue is replaced by "*Langue Plicaturée*" (fissured tongue). They do not maintain transformation to be absolute, but they acknowledge that it is

Fig. 2.—Simultaneous presence of geographic tongue and fissured tongue.

at least quite common. Out of 116 cases with geographic tongue, they found transition to fissured tongue in 7. Caratzali believes that geographic tongue may be a *"Prodrome obligatoire"* of fissured tongue.[8,9]

According to August Seiler, fissure formation on the tongue appears mainly at the end of the first childhood period and sometimes at the beginning of puberty, while geographic tongue is known to appear mainly in the first years of life.[10]

Summary and Conclusions

Observations done over a period of five years on 8305 children, among them 1246 cases of geographic tongue 775 of which were under the age of 2, are reported.

From observations on these 775 children, it can be concluded clearly that the presence of geographic tongue in itself indicates that the organism of a child reacts in a particular way to environmental stimuli. The skin of such a child reacts with seborrhoid phenomena more frequently than that of children without geographic tongue, while cases of eczema verum are rare in these children and at the same time the occurrence of spasmodic bronchitis, in their respiratory tract, is commoner than in children without the condition, but the spasmodic bronchitis is without eosinophilia and the phenomena disappear relatively easily. It can be distinguished from asthma that usually appears in children who had had atopic eczema. This indicates that children with geographic tongue have a peculiar constitutional type of reaction.

Most outstanding in children up to 2 years is the association between geographic tongue, seborrheic dermatitis, and spasmodic bronchitis. These three conditions form a triad. The association with anorexia, insomnia, strophulus, and respiratory affect cramps is much rarer.

On prolonged observations during three, five, and eight years, it was determined that 41 cases passed from geographic tongue to fissured tongue. This transition indicates that there is a connection between these two conditions. Geographic tongue appears mainly in the first period of childhood, and subsequently many cases pass into fissured tongue. In eight cases geographic tongue was observed simultaneously with fissured tongue.

62 Rothchild Blvd.

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Primary Staphylococcal Enterocolitis

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An increasing number of cases of staphylococcal enterocolitis, often fatal, have been reported in the past few years following major abdominal surgery and/or after the administration of antibiotics.[1] Earlier, before the introduction of antibiotics, cases of a similar nature occurring with or without surgery were reported, but no evidence was presented to indicate that they were caused by Staphylococcus aureus.[2,3] This may be due to the fact that most stool cultures in the past were performed using special bacteriological media designed to inhibit the growth of the Gram-positive organisms in the feces and thus failed to permit growth of Staph. aureus. In 1947 Selberg[4] reported a case of fatal staphylococcal enteritis in an infant receiving no antibiotics who was breast fed from a mother who had a staphylococcal mastitis. Cultures of the infant's stool yielded mainly Staph. aureus.

The clinical course and laboratory and pathologic findings in a child not receiving antibiotics who had a severe staphylococcal enterocolitis and apparently recovered from the severe cholera-like illness only to die three days later are presented with bacteriologic findings which bear on the source and pathogenic properties of the strain of Staph. aureus causing the illness.

Report of a Case

A 2½-year-old white girl was admitted to Strong Memorial Hospital because of fever, vomiting, and diarrhea. Three days prior to admission she had started to vomit and then developed a profuse, watery diarrhea and a fever of 104 F (40 C) and she failed to respond to symptomatic measures which were generally effective in many seemingly similar cases of a nonbacterial enteritis prevalent in the community at the same time. No one else at home was ill and no antibiotic had been given to the patient or her parents within the previous six months. On the day of admission, after appearing somewhat improved, her diarrhea became much worse with almost constant, watery stools, and she became comatose with a temperature of 107.2 F (41.8 C). She was taken to the emergency ward, where an incision was made to introduce intravenous fluids, and she was admitted to the hospital, where on examination she would rouse slightly after stimulation.

On admission she appeared dehydrated and her blood pressure was 88/44. Her abdomen was soft and she was having frequent watery stools. Since she had a leukopenia and the clinical picture suggested a possible enteric infection, she was started on chloramphenicol. The third hospital day she was still critically ill though slightly more responsive. However, she had developed a hypoproteinemia (1.75A/1.57G) and vigorous steps were required to correct this. A bacteriologic diagnosis was established at this point by finding a pure growth of Staph. aureus hemolyticus in her stools. Accordingly, the dosage of chloramphenicol was increased and erythromycin, neomycin, and penicillin were also given until the sensitivity tests revealed that the organism was insensitive to penicillin but sensitive to both chloramphenicol and erythromycin, at which time the penicillin and neomycin were discontinued. From the 5th to the 12th hospital day the patient showed gradual improvement with administration of fluids, salt-free albumin, a transfusion, and antibiotics. However, a gradual fall occurred in her hemotocrit to a value of 28% on the 11th day in spite of the transfusion. She began to take fluids orally on the 7th day, though she continued to have some diarrhea. With the antibiotics the normal fecal flora of Gram-negative bacilli did not reappear and on the 9th day yeasts predominated in her stools. Nystatin (Mycostatin) was administered orally and chloramphenicol was discontinued. Following this, Aerobacter aerogenes rapidly became predominant in her stools on smear and culture. On the 13th day she appeared lethargic but talked

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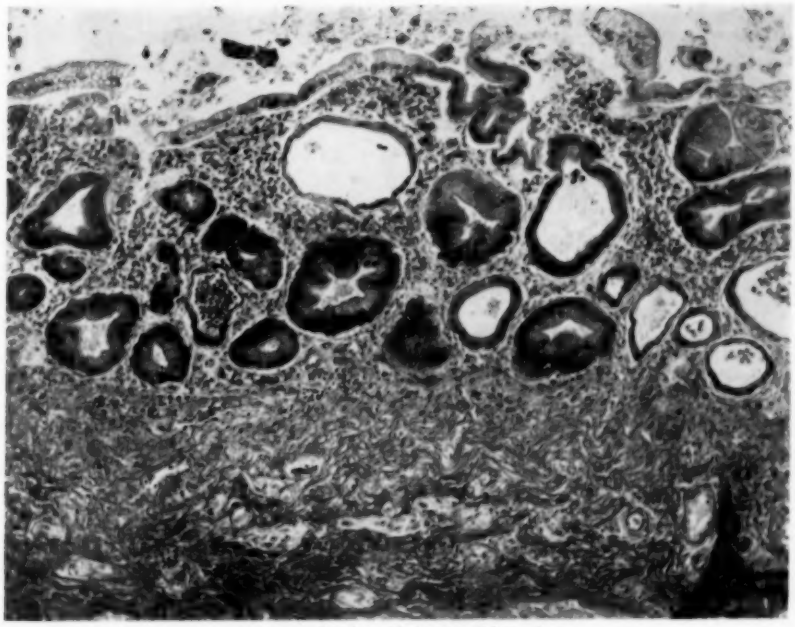

Fig. 1—Section of the small intestine.

Hospital Day	1	2	3	4	5	6	7	8	9	10	11	12	13
Responsiveness	0	+	+	+	+	+ +	+ +	+ +	+ + +	+ + +	+ + +	+ + +	+ +
Diarrhea	+ + + +	+ + + +	+ + +	+ + +	+ + +	+ + +	+ + +	+ + +	+ +	+	+	+ +	
Vomiting	+ + + +	0	+	+ +	0	0	0	0	0	0	0	+	+
WBC x 10^3	4.7	6.7	12.8	29.8	20.9	17.9	15.3		14.0		11.3		
Polymorphs %	few	30	88	88	74	81	68		67		58		
N P N mgm %	52		52	54	42	22				22			70
CO_2 meq / l	16.4	13.0	16.4	13.0	23.6	31.0	29.0			20.5			13.6
Na meq / l	134	136	127	123	125	138	137			136			139
K meq / l	4.0	4.1	5.6	4.4	4.4	4.6	3.1			4.4			6.0
Ca mgm %				5.6		6.5	6.5			7.3			10.0
P mgm %				2.0		1.3	1.3			1.9			8.2
Stool Culture		S. AUREUS + THROAT	S. AUREUS		S. AUREUS	FEW S. AUREUS	NO GROWTH	NO GROWTH	MONILIA	MONILIA & AEROG.	MONILIA & AEROG.	& AEROG.	& AEROG.
Gram Stain g+ cocci			+ + + +	+ + +	+	rare	0	0	yeast	yeast	yeast	0	
Gram Stain g- rods			rare	rare	rare	0	0	0	0	+	+	+ + +	
Chloramphenicol mgm i.m.		500	1000	1600	1000	1600	1600	1600	1600				
Erythromycin mgm p.o.			500	320	320	320	320	320	320	1000	1000		
Penicillin U x 10^6 i.m.			4	4									
Neomycin mgm p.o.			500										
Mycostatin mgm p.o.											500	500	

Fig. 2—Summary of findings in a case of primary staphylococcal enterocolitis.

freely and was well aware of her circumstances. While preparations were being made to administer parenteral fluids, she suddenly died.

At autopsy the body appeared poorly nourished and pale. The stomach and small and large bowel appeared grossly normal, and the mucosa was smooth, pink, and intact. The heart and liver were somewhat pale. The brain appeared grossly normal. Cultures of the intestinal contents revealed only Aerobacter aerogenes.

Microscopic findings of note were confined to the gastrointestinal tract. Multiple sections from various levels of distal jejunum and ileum all showed a similar picture of an architecturally disorganized, narrow mucosa composed of irregular, regenerating glands with numerous mitotic figures interspersed with somewhat dilated glands (Fig. 1). The surface layer of epithelium was intact, and the lamina propria contained numerous mononuclear and polymorphonuclear cells. Collections of polymorphonuclear leukocytes were also seen in many of the regenerating glands. In the colon changes were minimal. A mild degree of fatty metamorphosis was seen in the liver. The heart was normal and the adrenals only showed some decrease in lipids in the cortical cells. Gross and microscopic examination of the kidneys revealed no abnormalities. The anatomical diagnosis was subsiding acute enteritis with extreme mucosal regeneration.

Bacteriological studies revealed that the patient had a coagulase-positive hemolytic Staph. aureus in her throat and stool on entry, which was resistant to penicillin and tetracycline but sensitive to chloramphenicol, erythromycin, and bacitracin. A Staphylococcus with the same pattern of sensitivity to antibiotics was isolated repeatedly from her stools until the sixth hospital day. Cultures taken from the nose of the mother revealed a hemolytic Staph. aureus with the same spectrum of antibiotic sensitivity. Examination of these strains of Staph. aureus (i. e., from patient's throat and stool and mother's nose) by Dr. Lewis J. Griffith, of the Veterans Administration Hospital, Batavia, N. Y., revealed them to be the same bacteriophage type (31,44,44A,75,54). Furthermore, through the cooperation of Dr. Gail M. Dack, of the Food Research Institute of the University of Chicago, the cultures of Staph. aureus from the patient and her mother were shown to produce enterotoxin.

Comment

This patient developed a severe, cholera-like enterocolitis due to a drug-resistant hemolytic strain of Staph. aureus in the absence of antibiotic therapy or abdominal surgery. This organism was able to parasitize her gastrointestinal tract in the absence of these antecedent conditions which are common in such patients. It may be that she suffered from the nonbacterial enteritis that was epidemic in the community and that the consequent upset in her enteric bacterial flora made it possible for the Staphylococcus to emerge as the dominant organism and thus cause the severe enterocolitis. The same antibiotic-resistant Staphylococcus was isolated from her throat, her stool, and her mother's nose, as suggested by the same spectrum of resistance to antibiotics and confirmed by bacteriophage typing. This resistant organism was present even though neither the patient nor her mother had recently been hospitalized or had received antibiotics for the previous six months. This was an enterotoxic strain of Staphylococcus, and it appears likely that the production of enterotoxin in her gastrointestinal tract was responsible for her enterocolitis.

After apparently recovering from her illness and accepting oral feedings, the patient suddenly died with no apparent cause, since on gross examination postmortem her gastrointestinal tract appeared normal. Microscopic examination, however, revealed a marked disorganization of the intestinal mucosa with the disappearance of the normal villi and a marked reduction of the effective surface for absorption of nutriments. It appears likely that she suffered from some nutritional deficiencies.

The staphylococci in her bowel may have produced toxins which exerted their effects late to contribute to her death. However, microscopic examination of other organs revealed no significant changes to indicate their possible site and nature of action.

This case indicates that primary staphylococcal enterocolitis may occur because of drug-resistant organisms producing enterotoxin which spread by contact in a family. Such a patient may die after apparent recovery with a markedly abnormal intestinal mucosa that develops during the healing

process and which has lost its usual physiological efficiency as an absorptive surface for nutriments.

Summary

A 2½-year-old girl with primary staphylococcal enterocolitis due to drug-resistant, enterotoxin-producing organisms died after apparent recovery. Postmortem examination revealed a markedly disorganized enteric mucosa which possessed a reduced absorptive surface.

Mrs. Alice D. Leahy assisted in the bacteriological studies.

260 Crittenden Blvd.

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Pheochromocytoma in a Boy Aged Ten Years

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Pheochromocytoma is a tumor originating from chromaffin tissue, most frequently from the medulla of the adrenal gland. It secretes epinephrine and norepinephrine in variable amounts. The tumor is usually benign and occasionally malignant.[1] The majority of the tumors are unilateral without predilection for either side. Some are bilateral[7] and some extra-adrenal. Pheochromocytoma in childhood is rare but should be considered if renal disease can be excluded as the cause of hypertension.[9,15,19] The hypertension, which can be either sustained[13] or paroxysmal, is due to circulating norepinephrine.

In a recent review of the literature[16] Smid and Du Shane (1955) cite a total of 32 cases of pheochromocytoma in children of 14 years and under reported since 1910 of whom 9 were girls and 22 were boys. The sex is not stated in one case in which a medullary tumor was found at autopsy. The youngest child was 18 months, and 16 of the 32 were aged 10 or under. The tumor occurred in connection with the right adrenal in 10, the left in 8, both in 8, and was extra-adrenal in 9. In four of the patients extra-adrenal tumors were found as well as tumors in one or both adrenals. Operation for removal of the tumor was performed on 22 children. Eight died and fourteen recovered and remained well.

Report of a Case

A boy aged 10 years was admitted to the Southampton Children's Hospital on Oct. 22, 1954, under the care of Dr. G. Ormiston. He had suffered for six months from frontal headaches which were worse on exertion and associated with vomiting. On the night before admission he had had a particularly severe attack. He became disorientated and had three consecutive generalized epileptiform convulsions. There was no past history of any serious illness or kidney disease, nor was there a family history of hypertension. An uncle suffered from epilepsy.

The boy was well nourished, weighing 29 kg. (64 lb.), and was pale and unconscious. He was irritable when examined, moving his limbs freely. The pulse rate was 180 per minute. The heart was not clinically enlarged, and no murmurs were heard. The blood pressure was 90/60 mm. Hg. Examination of the lungs and abdomen revealed nothing abnormal. There was slight left facial paresis. The right biceps jerk was the only tendon reflex present. The abdominal reflexes were absent, and the plantar reflexes were extensor. The pupils were equal and reacted to light, and the fundi appeared normal.

The pulse rate dropped in a few hours to 120 and he became conscious and cooperative after some 12 hours. However, he was unable to see beyond the edge of the bed and within a few hours became totally blind, remaining so for almost 24 hours, after which he completely recovered his sight and improved in every way.

The cerebrospinal fluid, urine, and radiograph of the skull showed no abnormality.

The child was discharged home 11 days after admission with a provisional diagnosis of toxic encephalopathy. Ten days later he suffered a further severe headache and was readmitted. His blood pressure was now 120/90 mm. Hg.

The CSF was again normal as was also an electroencephalogram. X-rays of his long bones showed no lead lines. The blood urea was 22 mg. per 100 cc., and an intravenous pyelogram showed no anatomical or secretory defect.

Four days later his blood pressure was 150/90 mm. Hg and after that it remained consistently high, ranging from 125/100 to 180/150 mm. Hg, with marked day to day variation. (Fig. 1).

In the six weeks prior to operation he had four attacks of frontal headache lasting from early morning to late afternoon and associated with vomiting. In only two such attacks was his blood pressure raised above what it had been on previous days. The headaches were unaffected by acetylsalicylic acid (aspirin) or ergotamine. They were never associated with sweating or pinkness of the palms. He never complained of palpitations, but

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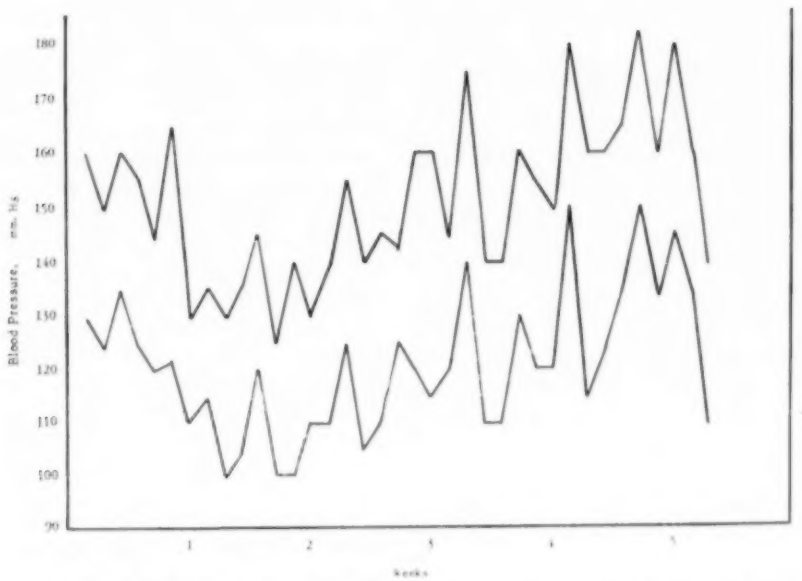

Fig. 1.—Chart showing day-to-day variation of blood pressure before operation.

sometimes during an attack the radial pulse was thready and difficult to count, although the rate was never raised, remaining constant at about 90.

Investigations

The urine examined weekly never showed protein, cells, or casts. The blood urea was never above 23 mg. per 100 cc. Two intravenous pyelograms showed both kidneys in normal position with apparently good function. These findings were considered to rule out renal disease.

Both femoral and both anterior tibial pulses were palpable. Blood pressure in the legs was 200/140 mm. Hg while that in the arms at the same time was 160/130 mm. Hg; these findings did not suggest coarctation of the aorta.

X-ray of the chest showed an unfolded aortic arch and a prominent left ventricle. Electrocardiograph tracings showed no abnormality.

Additional data were as follows:

Blood sugar	93	mg/100 cc.
Serum proteins		
Albumin	4.5	gm/100 cc.
Globulin	2.5	gm/100 cc.
Serum sodium	133	mEq. per liter
Serum potassium	4.3	mEq. per liter
Serum chloride	104	mEq. per liter
Serum alkali reserve	27.3	mEq. per liter

Twenty-four hours excretion of

1. Total neutral 17-ketosteroids (Tompsett) = 3.8 mg.
2. Cortiscosteroids (17-ketogenic, Norymbershi) = 6.9 mg.

Basal Metabolic Rate (corrected for age, etc.) + 33%.

The raised blood pressure, headaches, absence of renal disease, and intermittent nature of the symptoms suggested a pheochrome tumor, and the following tests were therefore carried out.

1. *Benzodioxan Test.*—An intravenous drip of isotonic saline was set up. The blood pressure was recorded at five-minute intervals until the level became stable at 145/115 mm. Hg; 11 mg. of benzodioxan (piperoxan) in a volume of 5 ml. water was then slowly injected through the tubing over a period of two minutes. After the injection the diastolic pressure fell by 15 mm. Hg but the systolic pressure remained un-

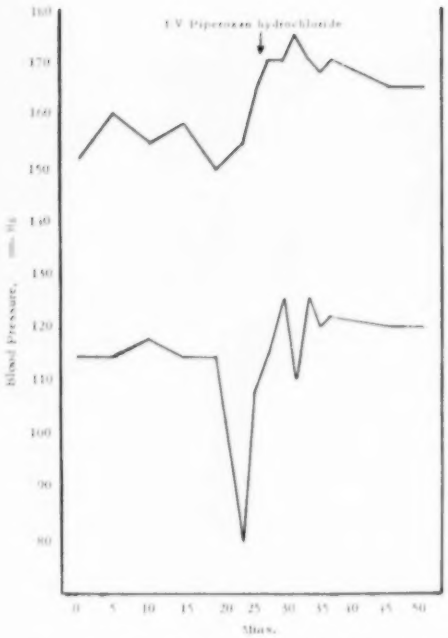

Fig. 2.—Chart showing fall of diastolic blood pressure after giving 12 mg. of benzodioxan intravenously over a period of two minutes.

changed. The pulse rate increased rapidly to 160 per minute, and the patient said he felt hot. Within five minutes the blood pressure level returned to 145/115 mm. Hg, but the pulse rate decreased more slowly.

It was decided to repeat the test using 12 mg. of benzodioxan. This time the diastolic pressure fell by 35 mm. Hg, but again the systolic level showed no change (Fig. 2). These results were considered to be equivocal.

2. *Presacral Retroperitoneal Pneumography.*—The triangular outline of the adrenals showed well on both sides but the outline of a tumor could not be established.

3. *Norepinephrine Excretion.*[11]—Two midstream specimens of urine were assayed biologically and found to contain 1.0 γg and 0.8 γg per milliliter of norepinephrine, respectively. Assuming urine excretion to be 1 liter in 24 hours, this meant an excretion of up to 1000 γg per day and confirmed the presence of a pheochromocytoma. Normal excretion for a boy of this age is about 30 γg per liter per day, and up to 300 γg per liter per day from an adult is considered to be consistent with essential hypertension.

Operation was decided upon and, in order to counteract any possible postoperative failure of adrenocortical secretion, three daily intramuscular injections of 50 mg. of cortisone acetate were given beforehand. After the operation the same dose was given every six hours for the first day and every eight hours for the second day. On the third postoperative day 25 mg. was given every 12 hours by mouth; 25 mg. was given by mouth once on the fourth day and a final 12.5 mg. by mouth once on the fifth day.

The anesthesia and management before, during, and after the operation were in the hands of Dr. V. P. Wordsworth. Premedication was with a mixture of the hydrochlorides of opium alkaloids (Pantopon) 10.00 mg. (1/6 grain) and scopolamine 0.200 mg. (1/300 grain). Induction was with thiopental (Thiopentone) sodium. Anesthesia was maintained with nitrous oxide, oxygen, and meperidine hydrochloride (Pethidine). Relaxation was obtained by intravenous tubocurarine chloride.

Before operation a cannula was inserted in the long saphenous vein near the ankle. A two-way connection was used so that either dextrose-saline (4.3% and 0.18%) or blood could be given as required. Alternative equipment was ready in case the first cannula should fail.

In order to control hypertension during the operation, phentolamine (Regitine) hydrochloride was available for intravenous use. To counteract hypotension after the tumor had been removed, a supply of levarterenol (Levophed) bitartrate was at hand.

While the surgeon was preparing the skin the patient suddenly stopped breathing and the blood pressure fell and could not be recorded. He recovered in about a minute, and the blood pressure rose to 140/120 mm. Hg; 1 mg. of phentolamine hydrochloride was given intravenously just before the

skin incision. A similar dose was given seven times during the operation. The blood pressure never rose above 175/160 mm. Hg, even when the tumor was squeezed. As soon as the venous return from the tumor was clamped the blood pressure fell. There was a further fall in pressure to 70/55 mm. Hg when there was bleeding from the inferior vena cava. Blood transfusion was started, and the blood pressure rose to 145/120 mm. Hg. Soon after this the norepinephrine (Noradrenalin) drip was begun, and for the remainder of the operation the blood pressure varied between 80/65 mm. Hg and 120/105 mm. Hg. The operation, including induction of anesthesia, took three hours. The patient was not moved from the theater until the blood pressure was steady at 100/80 mm. Hg and the general condition satisfactory.

Operation*

The choice of incision set a problem; preliminary laparotomy followed by incision in the loin of the appropriate side would technically have been easiest, but it would have required turning the patient. Even transfer from trolley (Gurney) to table brought about violent alterations in the blood pressure, so it was though advisable to avert turning the patient at all. A wide transverse muscle-cutting incision from one costal margin to the other was employed (Kvale, Priestley, and Roth, 1954[8]). The left half of the incision was made first, and the abdomen was explored; the left adrenal was normal, and the tumor was felt on the right side. Therefore the incision was completed. The liver was retracted upward, the hepatic flexure of the colon was retracted downward, and the duodenum with the head of the pancreas were mobilized and retracted to the left. The kidney was brought into view, and the tumor was easily exposed. There was a wide short vein in the anterior aspect of the tumor which drained directly into the posterior aspect of the inferior vena cava. After a little blunt dissection, the vein was exposed and clamps were placed on it. The vein was cut and ligatures were applied to the cut ends. The ligature on the side of the inferior vena cava slipped off and a large quantity of blood welled up into the wound; after considerable difficulty the bleeding point, about 3/16 in. in diameter, was found and tied off. The tumor afterward was easily dissected from its bed and removed; it was enucleated from the surrounding adrenal gland. There was no bleeding after the main vein had been secured. The wound was closed in layers.

The incision selected gave rather poor access to the right adrenal, and in an adult exposure would have been hampered by the chest wall. The child's elastic chest wall made retraction easy.

Postoperative Management

To maintain satisfactory blood pressure it was found necessary to continue the norepinephrine for 50 hours after the operation. At first it was given in a solution of 16 ml. of norepinephrine in 540 ml. of 5% dextrose, i.e., 32 γg per milliliter, and the rate was adjusted to keep the blood pressure between 100/80 mm. Hg and 110/90 mm. Hg. The balance of the salt and fluid requirements was given through the other branch of the cannula. Five hours after operation the norepinephrine was momentarily stopped; the blood pressure immediately fell and could not be recorded until the norepinephrine was given again. The same thing happened 20 hours later. The amount of norepinephrine required to maintain the blood pressure constant gradually decreased (Fig. 3), and after 50 hours the patient maintained his own pressure without norepinephrine.[18] Thereafter the pressure remained about 115/85 mm. Hg. No further blood transfusion was needed after the patient left the operating theater. Up to Oct. 31, 1955, he has remained completely well and with no recurrence of the hypertension or other symptoms.

* Performed by Mr. Tom Rowntree.

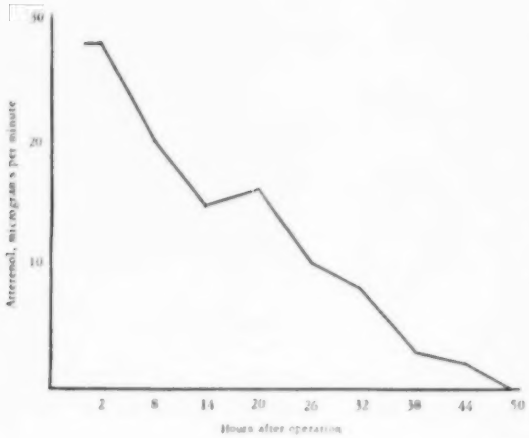

Fig. 3.—Chart to show the decreasing amount of norepinephrine needed to maintain the blood pressure between 100/80 and 110/90 mm. Hg after removal of the tumor.

Pathology Report

The tumor was circular in shape and about 3 cm. in diameter; it was clearly demarcated. A small piece of adrenal cortical tissue was included in the specimen. A few small cysts were present on the cut surface which showed variegated coloring, some areas being of notably dark appearance.

Histologically, the general appearance closely resembled adrenal tissue and consisted of noncompact groups of polygonal cells with quite large intervening vascular channels, associated with which were some areas of hemorrhage. The cells varied considerably in size and shape, and some showed vacuolation of the cytoplasm. Schmorl's silver staining showed the presence of chromaffin granules.

Comment

An interesting feature of this case was the unusual manner of presentation, in that the blood pressure was not found to be raised, so there was little to suggest the correct diagnosis. The differential diagnosis seemed to lie between cerebral tumor, epilepsy, migraine, and lead encephalopathy. It was only soon after the second admission, when hypertension was found, that the possibility of pheochromocytoma was envisaged. The system of differential diagnosis recommended by Rosenheim (1954) was used.[14]

Graham (1951) in an excellent and comprehensive review of 207 cases[5] states that the four commonest symptoms apart from hypertension are headache, palpitation, vomiting, and sweating, in that order. Two of these were present in our case. He also observes that some persons are susceptible to attacks after a period of rest, e. g., early in the morning. We were able to confirm this.

With regard to the value of the special investigations, the injection of benzodioxan or phentolamine[3,6,12] is relatively safe and easy and may be of great help. Perirenal air insufflation is dangerous. Presacral pneumography is safer and it did show the tumor in retrospect, but, judging from other reported cases, it is not of as much help as an intravenous pyelogram[15] or a straight x-ray.[17] The assay of urinary amines is the most useful test.[2,20] It is probable that fluorometric methods will be generally available in the near future.[4]

Laparotomy is justified if a tumor is suspected and is often essential to locate its position. Although removal of the tumor is a fairly hazardous procedure and requires careful planning, the risks are greatly decreased by expert anesthesia and by the use of adrenolytic drugs to counteract postoperative shock.[2,20]

Summary

A case of pheochromocytoma in a boy of 10 years, which presented in an unusual manner, is described. Details of the diagnosis, operation for removal, and pre- and postoperative management are given.

Dr. G. Ormiston, Senior Paediatrician at Southampton Children's Hospital and the Royal Hampshire County Hospital, Winchester, gave encouragement and help in the preparation of this paper. Mr. D. Willoughby, of University College Hospital, estimated the urinary amines, Dr. R. Caton supplied the radiographs, Dr. P. Farnan provided the pathology report, and Dr. E. Mellor, of St. James' Hospital, Portsmouth, supplied the EEG report.

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Transient Dysproteinemia in Infants

II. Studies of Protein Metabolism Using Amino Acid Isotopes

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The concentration of any constituent of the blood reflects the net balance between the rate of entrance of that substance into the blood and the rate at which it leaves the blood. Alteration of the concentration may occur as a result of a change in either or both rates. In order to gain better understanding of the mechanism responsible for the decreased concentration of plasma proteins in infants with idiopathic hypoproteinemia and anemia of a transitory nature, plasma albumin and globulin turnover rates have been measured in these infants as well as in normal infants.

With the use of isotopes it has been possible to measure the rates of isotope incorporation and disappearance of various in vivo systems. Plasma protein turnover rates have been calculated by various methods employing a tracer isotope. The results of these reported studies make it clear that the rates of synthesis and degradation of albumin and the various globulin fractions are different.[1]

There is incomplete agreement in the literature, however, concerning various methods employed measuring turnover times of the same plasma protein fraction.[1,2] The manner in which the protein is labelled appears to be of some importance. Protein may be labelled in vitro by iodination with I^{131} and the disappearance of radioactivity from the blood measured after intravenous administration. Several theoretical objections may be raised in criticism of this technique. Iodination introduces a foreign group into the protein molecule, and, in addition, the label may not be tightly bound. To overcome these objections, isotopically labelled amino acids have been fed or injected into man or animals with the expectation that certain of these labelled molecules will find their way into newly forming plasma protein molecules. Stable isotopes of nitrogen (N^{15}) and radioactive isotopes of carbon (C^{14}) and sulphur (S^{35}) incorporated into amino acids have been successfully used.[3-5] This procedure of using labelled amino acids has the theoretical advantage that the rate of amino acid incorporation into protein is in a system which is little affected by the presence of the tracer substance. The rate of disappearance of the isotope from the circulating protein should then reflect the existing rate of "biological decay" of the labelled protein. Reutilization of the isotope-labelled group influences the apparent rate of protein turnover causing an apparent deceleration of the biologic decay rate and thus prolongation of the "biological half-life." Less error of this type seems evident when plasma protein is labelled by feeding isotope-labelled amino acids to a donor, and injecting the donor's plasma protein into the test subject.[1] No direct information is available concerning rate of protein formation when this technique is used. It would appear,

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therefore, that no single technique is available which will give exact information concerning the exact amount of protein being formed in addition to the true rate of degradation of each protein fraction.

Since each protein fraction appears to have a different turnover rate, the proper separation of fractions must be accomplished before isotope analysis, lest the rate of one fraction be obscured by contamination with specific activity from another fraction of different rate. It is well known that chemical separation of plasma protein components is usualy not complete when tested by the more critical method of electrophoresis. However, each chemical method results in a reproducible degree of separation under carefully controlled laboratory conditions. More precise data on completely separated components are possible if isotope determinations are made on electrophoretically separated proteins. However, a high dose of isotope is needed to produce levels of specific activity great enough for accurate isotope determinations in each fraction when paper-strip electrophoresis is used. The quantities of isotope required for such studies become impractical for human use because they may exceed the safe limits of radiation dosage if radioactive material is used and are prohibitively expensive. The technique of in vivo plasma protein labeling has been successfully employed using small serum samples from small animals where the amount of isotope is large in comparison to the body weight.[6]

Using a sensitive gas-flow windowless counter, it was impossible to detect significant C^{14} activity directly from the most active samples in the experiments using C^{14}-labelled phenylalanine described below when 40λ of plasma was separated by paper electrophoresis. Other methods of electrophoresis which allow use of a greater quantity of protein may possibly overcome some of these difficulties, but their use was not attempted by us. Except for studies of gamma-globulin labelled with I^{131}, we are unaware of other studies of albumin and globulin turnover rates in infants or children as determined by isotopes.[7-9]

Subjects Studied

Two infants with idiopathic transient hypoproteinemia and anemia (Patients 1 and 2) were studied during the active phase of clinical disease. Patient 1 was a 7-months-old girl. She had been suffering from hypoproteinemia since age 4 months. At the time this study began the total plasma protein level was 2.8 gm. per 100 cc., with 1.9 gm. per 100 cc. albumin and 0.9 gm. per 100 cc. globulin. She was on a mixed diet containing pureed fruit, vegetables, meats, and infant cereal. A low sodium milk preparation containing 3.5% protein was given, as well as vitamin supplements.

Patient 2 was a 6-months-old boy who had had symptoms of hypoproteinemia since age 3 months. His total protein level in the plasma was 3.8 gm. per 100 cc., of which 2.8 gm. per 100 cc. was albumin and 1.0 gm. was globulin. His diet consisted of pureed fruits, vegetables, and lamb. Homogenized milk and a multiple vitamin supplement were also included. A third patient (Patient 3) was studied at the beginning of recovery from this same type of illness and again 18 months after clinical recovery. Detailed case histories and other related studies of these infants are reported in detail elsewhere.[10]

Two normal infants were also studied. Patient 4 was the 2-month-old male sibling of Patient 3. His health and nutrition were excellent, and his serum protein and hemoglobin levels were normal for his age. His diet was constituted of breast milk, as well as pureed cereal, fruits, and vegetables. Multiple vitamin supplements were given daily. His weight gain during the study period of five weeks was 1500 gm.

Patient 5 was a 3-month-old girl who was hospitalized because of congenital anomalies of the central nervous system. Nutritional state of this child was adequate, but weight gain in the first 2 months of life was slow due to difficulty in nursing. For several weeks prior to the study the feedings were taken well. The diet was a diluted evaporated milk formula, pureed cereal, fruits, vegetables, and meats, as well as a multiple vitamin supplement. Weight gain during the study period was 1000 gm.

Technique

Procedure for Measuring Incorporation and Disappearance Rates of Isotopes in Protein Fractions Following Injection of D,L 3-C^{14} Phenylalanine.—D,L-Phenylalanine 3-C^{14} was diluted in 0.85% saline solution so that 50 ml. contained the total dose of 50 μc of radioactivity (12.9 mg.

3-C^{14} D,L-phenylalanine).* This solution was then sterilized by heat in the routine manner used in this hospital for parenteral solutions. An intravenous infusion of this solution was administered to each subject over a period of approximately 15 minutes. One child (Patient 5) was given the isotope in a hypodermoclysis of 30 cc. of sterile isotonic saline solution. Venous blood samples were then obtained 24, 48, and 72 hours after this infusion, as well as at weekly intervals thereafter. Approximately 5 cc. of blood was obtained at each venipuncture. Sodium oxalate was used as an anticoagulant. Immediately after the blood was drawn, plasma and cells were separated by centrifugation. Albumin and globulin were separated by the method of Pillemer and Hutchinson using precipitation with cold methanol.[13] Each sample was then dialyzed against several changes of distilled water at 5 C over 72 hours. Electrophoretic analysis of samples separated by this method reveal that no albumin was present in the globulin fraction, but a barely detectable amount of alpha-globulin remains with the albumin. The protein fractions thus obtained were then lyophilized and brought to a stable dry weight in a vacuum desiccator. Aliquots of each sample were then combusted in duplicate or quadruplicate to CO_2 by the method of Van Slyke and Folch[12] and precipitated as a $BaCO_3$ film. Counting was done on a planchet of 4.9 sq. cm. surface area in a windowless gas-flow counting apparatus.† Each sample was counted for three periods of three minutes each. Corrections of the data were then made for background radiation as well as for thickness of the $BaCO_3$[18] for each sample of "albumin" and each sample of "total globulin."

* This dosage of C^{14} radioactivity has been approved for use in these studies by the Committee on Human Application of Radioisotopes of this institution.

† Tracerlab SC-16 Windowless flow counter and SC-18 Superscaler.

Results

Incorporation of C^{14} into Albumin and Globulin.—Maximum concentration of C^{14} in each protein fraction was apparent at 24 or 48 hours after injection of the isotope in all patients. Table 1 gives the average values of corrected counts per minute from carbon-14 activity per milligram of $BaCO_3$ derived from the combustion of albumin and globulin fractions during the experiment. Since no samples were taken earlier than 24 hours, it cannot be said that these samples represent the true peak concentrations of isotope incorporation. To make comparisons of the rate of amino acid isotope incorporated into each fraction, the formula for biological concentration coefficient (BCC) described by Shulman and Falkenheim[14] has been used. Provided corrections are made for physical decay rate of the isotope, this formula may be used with S^{35}-, N^{15}-, or C^{14}-labelled amino acids. The formula stated generally is as follows:

$$BCC = \frac{\text{amount of protein incorporated isotope/mM} \times 100}{\text{dose of amino acid isotope/gm. of body weight}}$$

Comparisons are made at the same time interval after feeding or injecting the isotope. In the five infants tested, comparison was made at 24 hours. The results of these calculations are summarized in Table 2.

TABLE 1.—*Summary of Average Corrected Counts per Minute per Milligram $BaCO_3$ from Albumin and Globulin in Two Normal Infants and Three Abnormal Infants*

	Albumin (CPM/Mg. $BaCO_3$)*								
Days after C^{14} dose	1	2	3	7	14	21	28	35	42
Subject									
4 (Normal ♂)	9.9	9.0	8.9	9.9	10.3	6.3	5.8		
5 (Normal ♀)	7.8	7.8	6.3	5.0	4.7	3.9	3.0	2.7	
3 (Normal ♀ 18 mo. after hypoprot.)	3.5	2.5	2.7	2.3	2.2	2.0	1.2		
2 (♂ hypoprot.)	6.9	6.5	6.4	5.6	3.3	2.7	2.1		
1 (♀ hypoprot.)	9.4	9.9	6.5	4.8	2.9	1.7	1.2		0.6
	Globulin (CPM/Mg. $BaCO_3$)*								
4	15.5	13.9	12.7	9.2	6.8	6.7	6.0	4.8	
5	14.1	11.1	9.5	5.2	3.2	2.5	1.8	1.5	
3	5.0	4.0	3.7	2.4	1.7	1.6	1.4		
2	8.1	7.2	6.1	3.4	2.3	1.5	0.9		
1	8.9	7.3	4.9	2.9	1.5	1.1	0.6		0.04

* Corrected for background radiation and thickness of the $BaCO_3$ film.

TABLE 2.—*Rates of Incorporation of C^{14} into Albumin and Total Plasma Globulin Twenty-Four Hours After Injection of Fifty Microcuries of 3-C^{14} Phenylalanine*

Pt.	Age, Mo.	Body Wt., Gm.	Plasma Concen., Gm/100 Cc.	Counts/Min. Administered	CPM* per Millimole	BCC	BCC† Corrected
Albumin							
3	26	14,100	4.2	25×10^6	688	3880	4221
4	2	4740	3.6	25×10^6	1946	3689	3440
5	2	4240	3.8	25×10^6	1533	2599	2588
2	6	7100	2.8	25×10^6	1356	3851	2703
1	7	7000	1.9	25×10^6	1848	5174	2457
Globulin							
3	26	14,100	2.1	25×10^6	983	5543	4731
4	2	4740	2.0	25×10^6	3047	5777	4606
5	2	4240	3.3	25×10^6	2772	3852	5167
2	6	7100	1.0	25×10^6	1302	4520	1837
1	7	7000	0.9	25×10^6	1749	4898	1791

* Corrected cpm/mg. $BaCO_3 \times$ M.W. $BaCO_3$.
† BCC$\times$ ——— plasma albumin or globulin (gm. per 100 cc.) in each infant / average plasma albumin or globulin (gm. per 100 cc.) in normal infants.

The two normal infants (Patients 4 and 5) showed calculated BCC's of 3689 and 2599 for albumin after injection of the isotope. Patient 3, when studied 18 months after recovery, was found to have a comparable rate of isotope incorporation into albumin at 24 hours of 3880. Calculation of the data from Patients 1 and 2, who were hypoproteinemic at the time of the study, resulted in BCC's of 5174 and 3851 for the albumin fraction. These figures seem reasonably similar, and it would appear that there is no great difference in the rate of incorporation of amino acid isotope into albumin between the hypoproteinemic infants and the normal infants when calculated by this method. If a difference does exist, the faster rate is shown by the infants with hypoproteinemia.

BCC's calculated for total plasma globulin yielded similar results concerning the rates of formation of this group of fractions in the normal and hypoproteinemic infants (Table 2).

This method of calculation, however, fails to take into account the reduced percentage of body weight that is represented by protein in the hypoproteinemic infants. If a correction is used which essentially converts this coefficient from "concentration of isotope per molecule of plasma protein" to "concentration of isotope in total circulating plasma protein" for each fraction, a greater variation occurs. The correction is made by multiplying the previously calculated BCC by the following ratio:

$$\frac{\text{plasma albumin (gm/100 cc.) in each infant}}{\text{av. plasma albumin conc. (gm/100 cc.) in normal infants}}$$

Globulin data has been similarly corrected using the values of plasma globulin concentration. Since the extravascular plasma protein is decreased in hypoproteinemia, this correction is wrong on the side of being generous to those patients with reduced serum protein concentrations.

This correction demonstrates that Patients 1 and 2 are actually utilizing a smaller fraction of the administered amino acid for plasma globulin formation than are the other infants. This decreased utilization, then, implies that a smaller total amount of plasma globulin is being formed. The percentage of the administered isotope per unit of plasma protein is roughly the same in these two children as in those with normal globulin levels. The limit of each new molecule of protein to accept phenylalanine into its structure may have been reached, however, and a greater total amino acid isotope incorporation could only occur if more molecules were synthesized.

The results of the calculation of uncorrected BCC's may be compared with those of Kelley et al., who performed similar experiments feeding S^{35}-labelled methionine to normal and nephrotic children.[15] In two

normal children who were older than the infants reported here, these authors reported values of 3199 and 2978 for the BCC at 24 hours. These values seem comparable to those reported here for both the normal and the hypoproteinemic infants. In spite of a comparatively normal rate of amino acid isotope incorporation per new molecule of protein, the abnormal infants reported here were not maintaining normal serum protein concentrations. This, of course, suggests a *relative* failure of plasma protein synthesis, since the existing rate is insufficient to correct the hypoproteinemia. The relative failure is better demonstrated when the rates of isotope incorporation are corrected for the existing plasma protein content of each infant.

Rate of Disappearance of C^{14} from Albumin and Globulin.—The proper method of interpretation of the data concerning the rate of isotope disappearance from each plasma protein fraction is open to some question. There is no way of differentiating the protein which is labelled immediately at the time of injection of the 3-C^{14} phenylalanine from the protein which gains a new label later. As this specific amino acid is released from tissue protein, a portion of it becomes available for plasma protein synthesis.

At the present time the technique of injecting or feeding amino acids labelled with isotopes is the most direct one available to estimate rates of plasma protein synthesis. Transamination reactions, reutilization of amino acid carbon fragments, "feed back" from other labelled body proteins, and other complex phenomena may play significant roles in modifying the calculated rates of synthesis as well as degradation. These findings, therefore, have been interpreted to be representative only of rate of isotope incorporation into and disappearance from plasma protein fractions. No attempt to determine actual amount of protein entering into or lost from the circulation seems justified. Such results, therefore, are valuable only on a comparative basis. Using another essential amino acid (lysine) labelled with radioactive carbon, Yuile and co-workers were able to demonstrate that the carbon label remains in the original amino acid almost entirely throughout the course of similar experiments.[16] It is likely, but not proved, that the "reutilization" label is still in phenylalanine and not in totally new carbon compounds which have entered the plasma proteins.

Various investigators have used different periods of time following the original injection of isotope to calculate the rate of "protein half-life." Regardless of which time period is used, it seems likely that some degree of error involving secondary incorporation of labelled amino acid into albumin and globulin is inevitable. In the early period following the injection of isotope-labelled amino acid, an unstable state is present due to the redistribution of labelled plasma protein during mixing with extravascular areas. In addition, labelled amino acids which have been released from other body proteins with rapid turnover rates are becoming available for incorporation into plasma proteins. Although reincorporation of previously utilized amino acids is probably at its lowest level during the first three days, these several factors make the early data less consistent and perhaps a less accurate reflection of degradation rate of each plasma protein fraction. In each infant studied, a steady rate of decline of the isotope concentration is not seen earlier than three days after the isotope injection. The later rate of decline can be plotted as the log of isotope concentration versus time.

The data from each plasma fraction of each subject was mathematically analyzed, and the disappearance rate was found to be an exponential one. A theoretical curve was calculated using the data after Day 7 by expansion of the equation, $Y = Y_o e^{-kt}$. Y = total isotope in the fraction; $Y_o = Y$ at

TABLE 3.—*Statistical Analysis Comparing Data with Theoretical Curves Used for Calculation of Half-Life*

Subject	Albumin				Globulin			
	N	F	Level of Significance (p)	$t_{1/2}$ (days)	N	F	Level of Significance (p)	$t_{1/2}$ (days)
1	10	32.41	0.001	12	8	28.33	0.001	10
2	8	12.75	0.005	15	8	51.50	0.001	11
3	8	18.93	0.005	23	8	9.50	0.01	28
5	10	7.00	0.01	29	10	14.40	0.001	16
6	10	2.75	0.10	22	10	7.12	0.01	33

N = Number of data points analyzed.

$$F = \frac{\sigma_1^2}{\sigma_2^2}; \text{ where } \sigma_1^2 = \frac{\Sigma (\text{data value} - \text{theoretical value})^2}{n-1}$$

$$\text{and } \sigma^2 = \frac{\Sigma (\text{data value} - \text{mean of data values})^2}{n-2}$$

time zero; k = coefficient of transfer out of fraction, and t = time. The variance of the individual data points from the theoretical points was calculated and compared with chance variations about the empirical mean. The data are significant at the 1% level with the exception of the albumin data on Patient 4. A summary of the statistical analysis is presented in Table 3.

Using the calculations for simple decay proposed by Solomon,[17] the half-life of each protein fraction can be calculated from this data by the formula $t_{1/2} = \frac{\ln 2}{k}$. In this equation $t_{1/2}$ represents the half-life of the protein. K may be calculated from the equation $k = \frac{\ln i_0 - \ln i_1}{t}$. In this equation i_0 is the concentration of isotope at the beginning of the isotope decay and i_1 is the isotope concentration at a later point in the experiment.

The rate of disappearance of isotope from the albumin fraction in these infants is shown in Figure 1. The rapidly disappearing components are evident in the data points representing the samples during the initial three days. The half-life of albumin in Patient 4 was found to be approximately 22 days. Patient 5 was shown to have a half-life of C^{14} in albumin of 29 days.

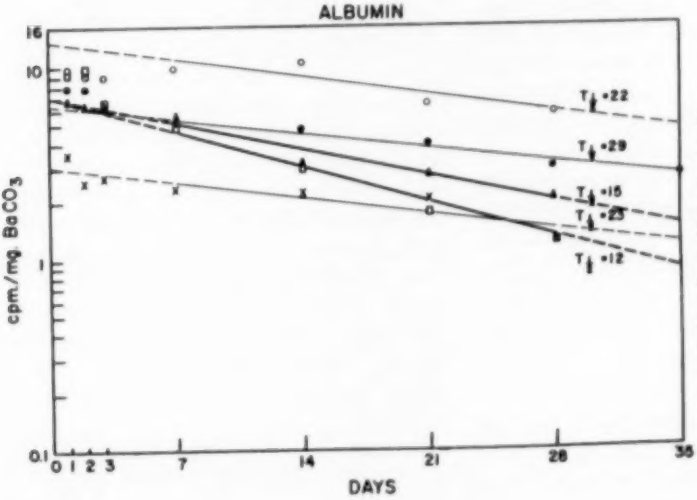

Fig. 1.—Rate of disappearance of C^{14} activity from "plasma albumin." The two heavy lines represent infants with hypoproteinemia. Dotted lines represent extension of the theoretical curves. ▲ & □ = hyproproteinemia and anemia (Patients 1 & 2); x = Patient 3; o = Patient 4, and ● = Patient 5.

These rates seem comparable to the majority of studies available in the literature pertaining to adults. Patient 3 who had recovered from hypoproteinemia 18 months prior to this study was shown to have a similar rate of disappearance of isotope from the albumin fraction. The calculated half-life of this patient's albumin was 23 days. Patient 2, who was hypoproteinemic at the time of the study, showed a more rapid turnover of isotope in the albumin fraction than the three previously mentioned infants. The finding of a half-life of approximately 15 days in this patient is below the range found in similar studies performed in normal adults. Patient 1 also demonstrated a rate of isotope loss from albumin ($t\frac{1}{2}$ = 12 days) which is considerably faster than has been previously recorded in normal adults using amino acid labelling, and is more rapid than the normal infants. The values for albumin half-life in these two patients seem significantly shortened when their clinical condition is considered. The serum albumin level of these children was low during the period of this study.

The rate of disappearance of isotopes from the globulin fraction was also measured in these patients. In addition to other factors previously mentioned which complicate precise interpretation of the data, it should be pointed out that fibrinogen was included in the globulin fraction of this study. It has been shown by other investigators that the rate of turnover of fibrinogen is considerably faster than that of any individual globulin fraction.[18] The data presented here, therefore, are comparable only from one person to another within this study, since no single plasma protein fraction is represented, and the rate of isotope disappearance is an algebraic summation of rates of various fractions known to be included.

The two normal infants (Patients 4 and 5) showed isotope disappearance rates in this fraction of 33 and 16 days, respectively. The older child who had recovered from hypoproteinemia (Patient 3) demonstrated a half-life of isotope in this fraction of 28 days. The hypoproteinemic infants (Patients 1 and 2) demonstrated half-lives of 11 and 10 days, respectively (Fig. 2). The differences between the patients with normal serum protein levels and those with hypoproteinemia are not striking. It was shown by electrophoretic analysis that the infants with hypoproteinemia had normal levels of plasma fibrinogen. It seems likely that a rapid turnover rate of fibrinogen could play a significant role in prolonging the half-life calculations determined here. Continuing rapid reincorporation of phenylalanine-3C^{14} into fibrinogen, as this amino acid again becomes available from the degradation of other labelled body proteins, could maintain a high isotope concentration in the "total globulin." It appears that the disappearance rate of "total plasma globulin" in the hypoproteinemic patients was slightly faster than that of the patients with normal plasma protein levels.

A Study Using N^{15} Glycine

The first child to be observed by our group with the peculiar syndrome of anemia and hypoproteinemia was studied in several ways to determine the state of her protein metabolism.[10] This child was found to be in positive over-all nitrogen and mineral balance. With the exception of a later onset of symptoms, the clinical course of this infant was quite similar to the two hypoproteinemic infants studied using C^{14}-phenlyalanine. This child was 7 months old at the time of onset of symptoms, and it was within the month after onset that the study being reported was performed. It appears from the clinical course that the child had already begun to recover at the time of this study. The edema was disappearing and the serum protein level was slowly rising. Anemia was present and unchanging.

Method of Study.—The child was fed a diet of milk alone for a short period of

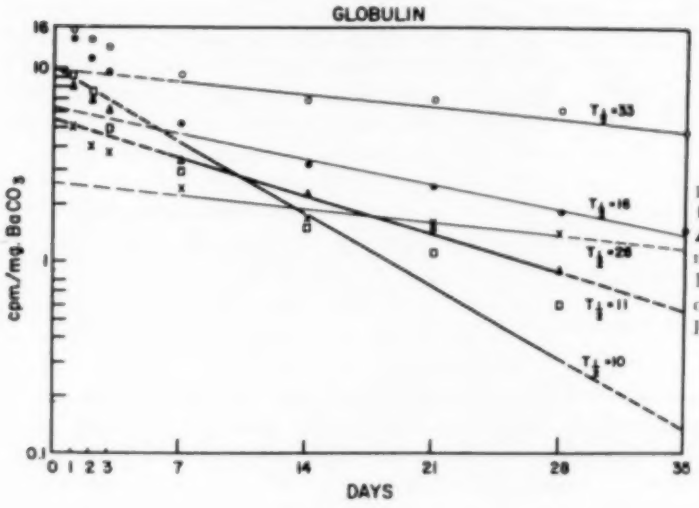

Fig. 2.—Rate of disappearance of C^{14} activity from "plasma globulin." ▲ & □=hyproproteinemia and anemia (Patients 1 & 2); x=Patient 3; o=Patient 4, and ●=Patient 5.

time; 150 mg. of glycine labeled with N^{15} was added to a small amount of the milk, which was fed at 8:00 a. m. The nursing bottle was rinsed thoroughly several times with small quantities of distilled water, and the child took these rinsings readily by mouth. Quantitative collections of the urine and stool were made in the ensuing 48 hours. Urine was collected by indwelling catheter in 6-hour aliquots during the first 24 hours and in a single aliquot in the second 24 hours. Carmine and charcoal were used to delineate stool periods. Blood samples were obtained at 4-hour intervals for 24 hours, and at 12-hour intervals during the following 24-hour period. Urine and stool samples were analyzed for their content of total nitrogen by the Kjeldahl method and for N^{15} in the mass spectrometer. Blood samples were analyzed for total plasma nitrogen, total proteins, and for N^{15} in each of these fractions.‡

Results.—Table 4 includes the results of the analysis of this patient's plasma for N^{15} concentration. Analysis for total protein N^{15} was made only on the first sample which was taken four and one-half hours after feeding N^{15}-labelled glycine. The amount of blood necessary for complete analysis of subsequent samples was prohibitive so that only total plasma N^{15} is reported at the later times. It is probable that the N^{15} in plasma after eight and one-half hours following ingestion of the labeled glycine is almost entirely in the protein fractions.

The BCC calculated for this patient in a manner similar to that used in the study of phenylalanine 3-C^{14} is 7475. This rate of isotope incorporation into total protein is more than twice the value found in the normal infants in the studies described earlier.

Analysis of the rate of disappearance of N^{15} from serum during the first 48 hours after ingestion shows that this rate has not yet reached equilibrium. Calculations by the

TABLE 4.—*N^{15} in Plasma Following Oral Administration of 150 Milligrams of Glycine-N^{15} Patient Three, Seven-Month-Old Girl with Hypoproteinemia and Anemia*

Time (Hr.)	Atoms % Excess N^{15} in Total N	Atoms % Excess N^{15} in Total Protein
4.5	0.0360	0.0134
8.5	0.0313	"
11.75	0.0287	"
23.75	0.0252	"
36.0	0.0262	"
47.25	0.0230	"

‡ The N^{15}-labeled glycine and the analyses were supplied by Dr. L. Zeldis.

TABLE 5.—*Urinary N^{15} Excretion Patient Three, Seven-Month-Old Girl with Hypoproteinemia and Anemia*

Time (Hr.) After Ingestion*	N^{15} in Urine (Mg.)	Excretion % of Admin. Dose	Amount Retained (Mg N^{15})
6	3.190	16.8	16.41
12	1.740	9.1	14.67
18	0.612	3.2	14.06
24	0.541	2.85	13.5
48	1.228	6.46	12.3
Total	7.311	38.4	12.3

* Labelled glycine administered = 19.6 mg. N^{15}

same methods previously applied to the phenylalanine C^{14} study show the data to be a heterogeneous group, and no half-life can be calculated. The study period was limited to 48 hours so that no conclusions can be made from this part of the experiment.

Urinary excretion of N^{15} was similar in rate and amount to that reported by Sprinson and Rittenberg in adults on normal protein intakes.[3] In 24 hours a total of 6.08 mg. of N^{15} appeared in the urine (Table 5). In the second 24-hour period an additional 1.23 mg. was excreted, totalling 38.4% of the ingested dosage over the 48-hour period. Since this labelled dietary amino acid was lost from the body at a rate comparable to that of normal adults, there appears to be no evidence for a failure of utilization of dietary glycine for protein formation. No N^{15} was detectable in the stools. Unfortunately, no comparable data concerning children are available. This finding, together with the finding of a high ratio of total urinary nitrogen to total dietary nitrogen,[10] suggests that a rapid rate of endogenous protein breakdown accompanying a normal rate of protein synthesis from dietary protein is the mechanism resulting in the low concentration of serum proteins in this patient. If the failure to maintain normal circulating levels of protein were on the basis of poor utilization of dietary nitrogen, the fraction of N^{15} appearing in the urine during this 48-hour period would be expected to be higher. The nitrogen from glycine is excreted rapidly when total protein nitrogen intake is high in comparison to rate of body protein synthesis. An analogous finding has been previously demonstrated using glycine N^{15} in subjects receiving a high protein intake.[3]

Interpretations

It seems apparent from the data presented here that the two infants with hypoproteinemia were incorporating amino acid isotope into albumin and globulin at a rate which was comparable with that of the normal infants. Since this comparison was made on the basis of a ratio of specific activity to weight of stable element of each protein fraction, we are essentially comparing the rate of entrance of amino acid molecules into a given protein molecule. When it is considered that these hypoproteinemic infants have fewer protein molecules in their bodies, it is apparent that a given dose of amino acid is not as completely utilized for plasma protein production as it would be if the number of protein molecules were greater. One might say that the efficiency per molecule is the same, but the efficiency per child is impaired in the hypoproteinemic infant. In addition to this the rate of disappearance of isotope-labelled amino acid from plasma protein is greater in the hypoproteinemic infants than it is in the infants with normal plasma protein concentration. If the rate of total plasma protein formation were assumed to be the same in these infants as in normal infants, this shortened half-life alone would result in a lower concentration of the circulating albumin. It appears, therefore, that the hypoproteinemia in these infants is associated with some degree of inefficiency of incorporation of amino acid into plasma protein in addition to a more rapid degradation rate of the protein once it is formed. These patients were studied thoroughly for clinical evidence of inflammation and none was found. It was also determined that there was no evidence of hyperfunction of the

adrenal cortex. The protein intake was well within the normal range at the time of these studies, as well as during the period when the hypoproteinemia was developing. Experiments in dogs fed diets adequate in calories but deficient in protein have demonstrated that the turnover rate of the existing plasma protein is considerably accelerated, especially that of albumin.[19] This is similar to the albumin turnover studies in our subjects with hypoproteinemia. The findings in the hypoproteinemic infants suggest that it is not mere inhibition of plasma protein formation from dietary amino acids causing the low serum protein level, however, but that some force at the site of destruction of protein or some factor within the protein molecule itself is altered in addition.

The number of abnormal conditions in man in which the turnover rate of protein has been studied is limited. It is therefore not surprising that this pattern of normal or slightly decreased protein synthesis together with rapid degradation has not been previously described. Interpretation of the results in terms of a basic etiology, therefore, is impossible.

That this state of hypoproteinemia and anemia is a temporary one seems to be borne out by the study on Patient 3 after her recovery as well as by the apparent clinical recovery of each of these patients. The studies of the albumin and globulin fractions of Patient 3 after recovery appear to be quite similar in all respects to those of the two normal infants and seem comparable with protein dynamic studies performed in adults.

The study performed on Patient 3 during the early recovery period demonstrated a greater rate of amino acid isotope incorporation into total protein than was seen in any of the other studies. It is not known whether this increased rate is due to a difference inherent in the two techniques of study or whether the recovery of this patient from her hypoproteinemia was occurring as a result of the more rapid rate of generation of proteins that this calculation would suggest. Although the value for the per cent of isotope appearing in the urine of this patient suggests that no rapid elimination of dietary amino acid is occurring, it does not seem safe to speculate that this state existed in the other patients studied. Since this infant was making a clinical recovery at the time of the study, her state of protein equilibrium was undoubtedly different in many aspects. The continuing high ratio of total urinary to total dietary nitrogen is perhaps accounted for by the continuing rapid degradation of the serum proteins. Recovery is occurring in spite of this by virtue of a high rate of protein formation from dietary amino acids.

The possibility has been considered that a deranged molecular structure of the protein fractions may be influencing the rapid degradation. It is not known whether the production of protein molecules by the fetus, other than hemoglobin, is different on a qualitative basis. Fetal hemoglobin is a qualitatively different protein which is no longer produced normally in significant amounts after birth.[20] The fetal hemoglobin which has been produced before birth disappears from the circulation as the red blood cells containing it undergo gradual destruction. In certain abnormal hematological conditions the persistent synthesis of fetal hemoglobin accompanies other abnormalities in the red blood cell. It seems conceivable that persistent postnatal production of a fetal type (or molecularly distinct) plasma protein could result in the abnormalities found in the protein degradation rates presented here.

An attempt, by using immunological techniques [10], to demonstrate a qualitatively different type of albumin in these patients during hypoproteinemia is in progress using yielded negative results. No differences from the normal have been found in electrophoretic mobility. A qualitative difference of the other plasma protein fractions which were depressed in the hypoproteinemic pa-

tients is also a possibility. This hypothesis is unproved at the present time.

Summary and Conclusions

A study of the rates of synthesis and degradation of plasma, albumin, and globulin during the active phase of hypoproteinemia and anemia in two infants is presented. Studies performed on one infant during recovery and 18 months after complete clinical recovery from idiopathic transient hypoproteinemia and anemia are also presented. The findings in these patients are compared with those obtained from the study of two normal infants using similar techniques. The rate of incorporation of C^{14}-labelled phenylalanine into albumin and globulin was similar in all of these children when calculated according to the biological concentration coefficient of Shulman and Falkenheim, with one exception. One infant who was studied during the recovery phase demonstrated a rate of incorporation of isotope into plasma protein nearly twice as great as the other infants. With this exception the normal and hypoproteinemic infants reported in this study demonstrated rates of amino acid isotope incorporation into plasma protein similar to that found in normal young children by other investigators. However, when this rate is corrected for the decreased total plasma protein mass in the children with hypoproteinemia it appears that the total amount of isotope-labelled amino acid incorporated into plasma protein is less in the abnormal infants than in those with normal levels of serum proteins. The rates of degradation of albumin and globulin fractions as estimated by this method are of the same magnitude in the normal infants as has been previously recorded in normal adults using various amino acid isotope labels. A more rapid turnover of both albumin and globulin as evidenced by a shortened half-life of isotope activity in each was demonstrated in the infants with hypoproteinemia. The rate of disappearance of isotope from the "total plasma globulin fraction" of the hypoproteinemic infants was not definitely different from that found in this globulin fraction of the normal infants. Since the fibrinogen content of the plasma was not depressed in the patients with hypoproteinemia, inclusion of this fraction in the analysis may have influenced the data to mask an even more rapid turnover rates of the alpha-, beta-, and gamma-globulin fractions. It appears that the hypoproteinemia in the patients studied here resulted from a *relative* failure of utilization of amino acids in addition to a rapid degradation of plasma proteins. It seems unlikely that the rapid degradation of the protein is related to a deficiency of some essential protein component in the diet of these children. This conclusion is supported by evidence previously presented regarding the good dietary intake of these patients preceding and during the development of hypoproteinemia and anemia. The possibility that this syndrome of transient hypoproteinemia and anemia is the result of an endogenous or conditioned derangement of protein metabolism seems more likely. Further investigation of the molecular structure of the serum proteins as well as other factors influencing protein metabolism seems necessary to establish the basic reason for the rapid degradation rate of proteins in these children. The etiology of this aberration in the rate of protein synthesis and destruction remains unknown at the present time.

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Acute Intrathoracic Gastric Dilatation Associated with Bochdalek Hernia in an Infant

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One of the congenital defects which usually is manifest in the earliest hours of life is the posterolateral diaphragmatic hernia through the foramen of Bochdalek (persistent pleuroperitoneal canal). Cyanosis and dyspnea may be present during the immediate postnatal period, and the presence of either should make one aware of the possible existence of a diaphragmatic defect with displacement of abdominal viscera into the pleural cavity. Once feedings are attempted emesis may become prominent and the other symptoms are exaggerated. Occasionally with diaphragmatic defects no symptoms are present and the lesion goes unrecognized for many months or years. In rare instances incarceration or strangulation of stomach or intestine occurs in posterolateral hernias and the patient presents an acute problem in diagnosis and management.

The present case is that of a 6-week-old boy with apparently normal postnatal development who suddenly had incarceration of his stomach through a posterolateral diaphragmatic defect with acute dilatation and rapid clinical deterioration.

Report of a Case

A full-term infant was delivered spontaneously Feb. 29, 1956. The birth weight was 2940 gm. Minimal cyanosis of hands and feet was noted during the first 24 hours of life, but this cleared readily. The remainder of the physical examination after birth was normal, including heart and lungs. Development seemed normal for the first 6 weeks without any observed feeding or respiratory tract problems. On April 17, 1956, shortly after taking the noon feeding the child began to cry loudly and rapidly became cyanotic with marked dyspnea. The child was brought to the Emergency Division. On admission he was noted to be a well-nourished baby with mottled blue skin and markedly cyanotic lips and nailbeds. The eyes were rolled upward; the neck was flaccid. Moderate inspiratory retraction of supraclavicular and subcostal areas was noted. The left chest was hyperresonant with absent breath sounds. Bronchovesicular breath sounds were present on the right side. Cardiac dullness extended far to the right. The heart was slow and irregular in rhythm and the sounds of poor quality. The liver was palpable to the level of the umbilicus. Admission weight was 5130 gm.

A roentgenogram of the chest revealed a markedly dilated stomach in the left chest with mediastinal shift to the right (Fig. 1). A small caliber plastic tube was quickly passed through the esophagus into the stomach, and after evacuation of 50 cc. of formula and 150 cc. of air the baby's pulse and respirations quickly became normal with return of the mediastinum to the midline. Fluoroscopy at that time revealed what appeared to be normal diaphragms with normal motion. The left lung was well-expanded and the heart was in the midline (Fig. 2). A gastroduodenal roentgenogram using very thin barium was done. Rapid canalization of the esophagus leading into what appeared to be a supradiaphragmatic stomach was seen. The latter apparently entered the chest through a posterolateral diaphragmatic defect (Fig. 3).

Operation was undertaken after placing a polyethylene catheter into an arm vein for fluid administration. A left paramedian abdominal incision was made under general endotracheal anesthesia. Upon entering the peritoneal cavity it was evident that a diaphragmatic hernia of some magnitude was present. The herniated viscera included stomach, spleen, colon, and a portion of small intestine, which were all reduced with ease. The posterolateral diaphragmatic defect thus exposed measured 3×3×2 cm. with the base on the chest wall. There was no peritoneal sac. The left lung was well visualized and expanded normally. No malrotation of abdominal contents was present.

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From the Thoracic Surgical Service, Yale University School of Medicine.

Fig. 1.—Admission chest roentgenogram showing markedly dilated intrathoracic stomach.

Easy repair of the defect was carried out, the patient withstanding the entire procedure nicely. An easy layer closure of the abdominal wall was possible. Immediately postoperatively a chest roentgenogram showed good lung expansion (Fig. 4). After operation there was heard for the first time a Grade III blowing systolic murmur loudest over the base and transmitted into the back. The electrocardiogram, however, was normal. Despite the murmur, the course after operation was benign, oral feedings being started after persistalsis was well established on the third postoperative day.

Fig. 2.—After gastric aspiration the left lung has expanded and the mediastinum has returned to its normal position.

Prior to the patient's discharge from the hospital an upper gastrointestinal roentgenographic series was normal (Fig. 5). The cardiac murmur was still present, but examination three weeks after operation revealed that it had almost disappeared.

Comment

Although a large congenital diaphragmatic defect usually presents dramatic symptoms, these do not always appear in the neonatal period. A recent case at this hospital was a 26-year-old man with a massive Bochdalek hernia in whom symptoms had been minimal despite the presence of a large portion of colon, small bowel, and stomach in the left chest. The present case is a good example of symptomatology delayed in onset and of life-endangering severity. The differential diagnosis of shock with dyspnea, bradycardia, and absent breath sounds on one side may be difficult. In general the choice is between spontaneous pneumothorax (usually of the tension type) and diaphragmatic hernia with mediastinal shift and lung compression. The wisdom of avoiding needle aspiration of a silent chest is emphasized strongly in the present case. Simple inser-

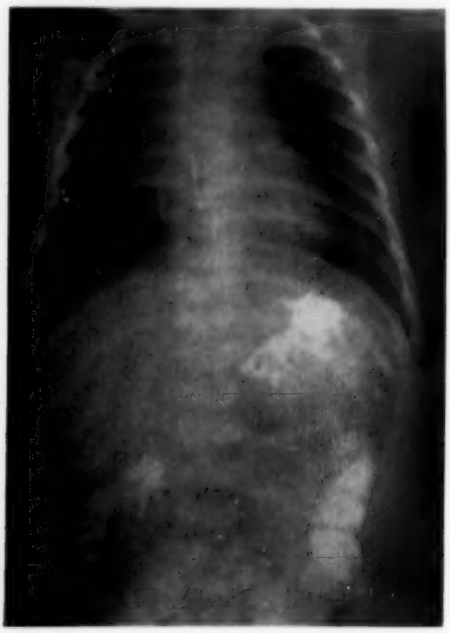
Fig. 3.—Barium ingestion reveals the stomach to be intrathoracic.

tion of a nasogastric tube appears to be a much wiser maneuver when one is not sure of the diagnosis. Certainly no harm can result from this procedure even if a pneumothorax is present, and if intrathoracic acute gastric dilatation is the basic problem rapid control may be effected. If unsuccessful, thoracentesis may then be performed and the few seconds expended in aspirating the stomach will not have constituted a harmful delay. It is not necessary to point out the possible sequelae of transthoracic needle puncture of a dilated stomach—empyema being the most important one. If the patient's condition permits, rapid chest roentgenography of course is invaluable in establishing the proper course of therapy.

It is interesting that complete reduction of the herniated stomach here occurred after initiation of gastric aspiration yet the barium study one hour later revealed return of the stomach into the chest. Evidently filling of the stomach with barium precipitated herniation again. At the time of operation anesthetic relaxation was probably responsible for further herniation of spleen, colon, and small intestine into the chest.

Fig. 5.—Normal upper gastrointestinal roentgenogram prior to discharge from the hospital.

Fig. 4.—Immediate postoperative chest roentgenogram reveals barium in the small bowel having been released from entrapment in the intrathoracic stomach.



The mechanism for production of the cardiac murmur after operation is not clear. It was perhaps originally masked by the herniated viscera. Sudden mediastinal shift after the herniation was established may have altered the course of the blood flow through the heart. With the passage of time, normal hemodynamics were established and the murmur then cleared.

Summary

A case of a 6-week-old child is reported with a large Bochdalek-type diaphragmatic hernia. The first symptoms were those of acute cardiorespiratory collapse associated with dilatation of the intrathoracic stomach following a normal neonatal period. The advisability of immediate decompression with a nasogastric tube in any case of shock associated with absent breath sounds in one hemithorax is illustrated by this case.

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Development of Sulfadiazine Resistance During an Outbreak of Shigellosis Due to Shigella Sonnei Form I

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The efficacy of sulfadiazine in the treatment of Shigella infections, where the organism is sensitive to sulfonamides, has been well established,[1-3] and because of its relatively low toxicity and general availability it has appeared to be the drug of choice in shigellosis therapy.[3] However, the problem of the development of sulfonamide-resistant strains was recognized in these early reports and independently reported by others.[4] In recent years several investigators have reported outbreaks in which resistant strains have either predominated or have been the only strains isolated.[5-7] Hardy's report,[3] however, is the only one which has come to our attention which demonstrated the development of resistant strains during an outbreak, with the subsequent spread of sulfonamide-resistant infections in the study population.

An unusual opportunity to study the development of sulfadiazine resistance was afforded us by an outbreak of shigellosis due to Shigella sonnei Form I in an institution for the mentally retarded. All children age 6 through 13 years admitted to this institution from August, 1953, to January, 1954, were placed under study as part of a Shigella flexneri type 3 vaccination project.* In accordance with the experimental protocol, rectal swabs were obtained from each child on a regular schedule so that cultures were done on each of 3 successive days during the week following admission and, beginning one month later, cultures were obtained at biweekly intervals for 12 weeks. During the latter part of the study additional specimens were obtained from some children.

The S. sonnei outbreak began during the 13th week of observation and continued for approximately 15 weeks. It was confined mainly to the boys' receiving ward where 40 of 61 children admitted to the vaccine study became infected. During the first three weeks of the epidemic most of the children with positive cultures were not treated with chemotherapeutic agents, but after the third week children with positive cultures, with or without accompanying diarrhea, were treated with sulfadiazine, 2 grains or 120 mg. per pound per day divided into four equal doses or a maximum of 2 gm. of sulfadiazine every six hours for five days. However, this basic regimen was frequently altered because of clinical necessity and some patients received less than the full course of therapy. When sulfadiazine resistance became apparent, chloramphenicol was substituted for sulfadiazine because of the favorable results obtained by Cooper and Keller[5] and Garfinkel and co-workers,[6] with the use of chloramphenicol in sulfadiazine-resistant infections. The usual dosage used was 250-500 mg. every six hours for five days.

Materials and Methods

The S. sonnei Form I strains were isolated as described by Croft and Miller* from plates of MacConkey (Difco) and S S (Shigella Salmonella) (Difco) media streaked with the rectal swabs and were identified by slide agglutination

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From the Division of Communicable Diseases, Ohio Department of Health.

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tests with specific antisera.† Agglutination occurred with Form I agglutinating serum but not with Form II. Difco sulfadiazine discs of 10, 50, and 250 mg. concentrations and chloramphenicol (Chloromycetin) discs of 10, 30, and 60 μgm. concentrations were used for the sensitivity determinations. The organisms were grown in heart infusion broth for 24 hours and then streaked on Mueller-Hinton (Difco) plates according to the directions of the disc manufacturer. Readings were made after 12 to 16 hours' incubation at 37 C. Cultures designated as sulfadiazine sensitive were inhibited by the lowest concentration disc used. One culture, which has been designated as "partially resistant" was resistant to the low concentration disc but sensitive to the higher concentrations. The other cultures designated as "partially resistant" showed the presence of resistant variants growing within the zone of inhibition surrounding the discs. Resistant cultures overgrew the discs completely.

Results

The results of the sulfadiazine sensitivity studies are shown in the Figure. The results of the chloramphenicol sensitivity tests are not shown, since the cultures were uniformly sensitive and inhibited by the lowest concentration of the drug.

S. sonnei organisms were first isolated during the 13th week of culturing. During the 13th, 14th, and 15th weeks, 12 children were found to have positive cultures, all of which were sulfadiazine sensitive. During the 16th week, five new infections were found, one of which showed a "partially resistant" culture. From the 17th through the 22d week 23 new cases occurred, 9 with sensitive, 2 with "partially resistant," and 10 with resistant organisms. Isolates from the seven new infections which occurred from the 23d through the 28th week were resistant. From the 29th through the 33d weeks no positive cultures were obtained, but during the 34th through the 36th weeks six children who had previously had positive cultures and who had been negative for 7 to 14 weeks again showed positive cultures, all of which were sulfadiazine-resistant.

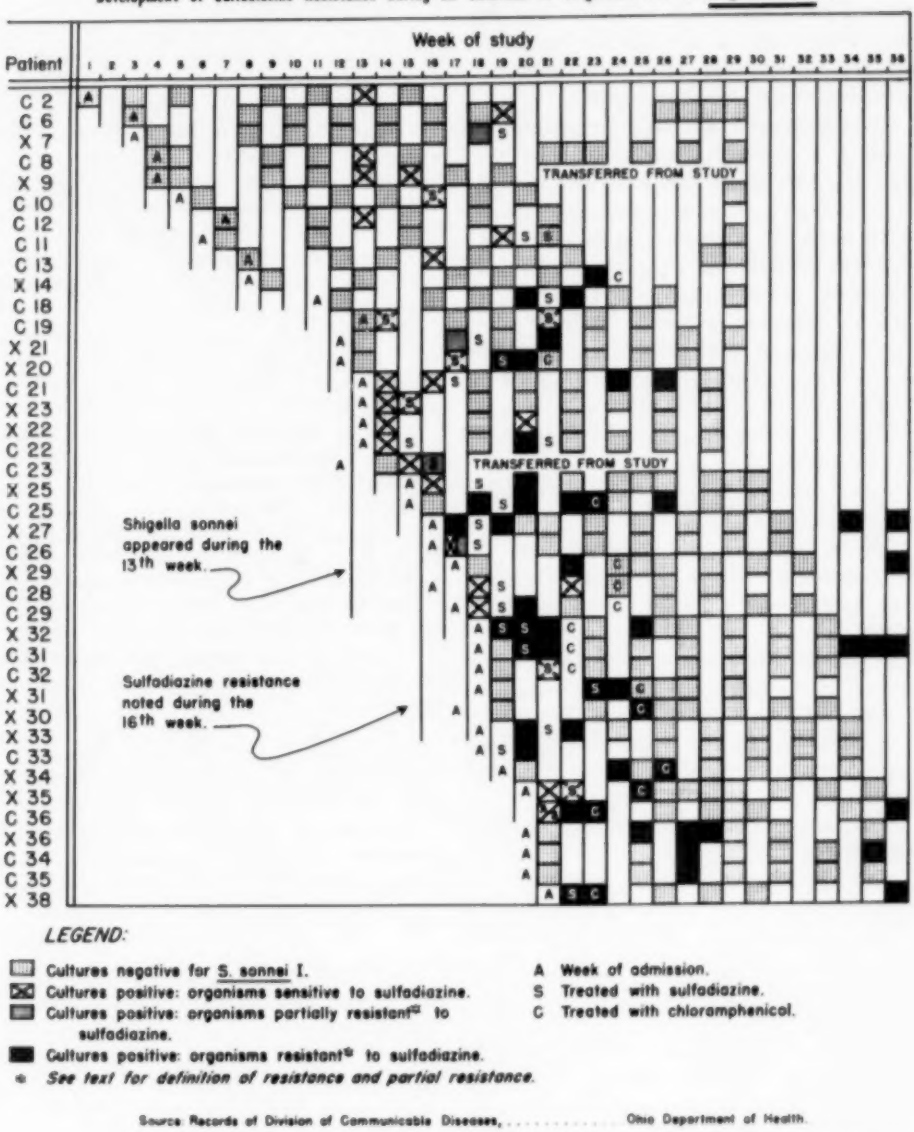
Comment

These results are interpreted as evidence of the appearance of sulfadiazine-resistant strains during an outbreak of Shigella sonnei Form I. The fact that patients who had initially sensitive strains subsequently excreted "partially resistant" strains prior to the demonstration of resistant strains in newly admitted patients suggests that the resistant strains developed from initially sensitive strains as the result of therapy. However, the possibility must be entertained that the resistant strains did not develop from the initially sensitive strains but were introduced from the outside as resistant strains, and that two distinct epidemics, one with sensitive strains and one with resistant strains, occurred simultaneously. In any event it is clear that during the period in which sulfadiazine was used as therapy the sensitive strains gradually disappeared whereas the resistant strains persisted and spread. During the last five weeks of the epidemic only resistant strains were isolated from newly infected patients.

It is interesting to note that six patients with resistant strain infections began to excrete organisms after their stools had been negative for several weeks. Whether these patients should be considered bacteriologic relapses or reinfections is not clear, as adequate isolation of cases was not carried out and ample opportunity for reinfection existed. However, it is certain that on the basis of several negative stools these patients would ordinarily have been transferred from the receiving unit to the various cottages of the institution and would probably have served as the source of infections in new areas of the institution.

The introduction, or the development of sulfonamide-resistant strains of Shigella during institutional outbreaks may present

† The initial isolation and identification of the Shigella strains used in this study were made by Raymond E. Daniels, Mary Jean Miller, and Dr. C. C. Croft of the Division of Laboratories, Ohio Department of Health using specific antisera supplied by Dr. W. H. Ewing of the Laboratory Branch, Communicable Disease Center, Chamblee, Ga.


Development of Sulfadiazine Resistance During an Outbreak of Shigellosis Due to Shigella sonnei I
Week of study
Patient
TRANSFERRED FROM STUDY
TRANSFERRED FROM STUDY
Shigella sonnei appeared during the 13th week.
Sulfadiazine resistance noted during the 16th week.
LEGEND:
Cultures negative for S. sonnei I.
Cultures positive: organisms sensitive to sulfadiazine.
Cultures positive: organisms partially resistant* to sulfadiazine.
Cultures positive: organisms resistant* to sulfadiazine.
* See text for definition of resistance and partial resistance.
A Week of admission.
S Treated with sulfadiazine.
C Treated with chloramphenicol.
Source: Records of Division of Communicable Diseases, Ohio Department of Health.

real problems for those who are responsible for control of the epidemics. Antibiotics which might be effective in the control of these organisms are in general more expensive than the sulfonamides, and their extensive use might well represent an intolerable financial burden to the institution. Although it would appear that the eventual development of sulfonamide-resistant strains is inevitable, it is probably wise to attempt to delay their appearance by using the maximal dose of the drug with the aim of eradicating all Shigella from the intestine.[9] Carefully followed isolation procedures may assist in minimizing the hazard presented by the resistant strains.[3] Careful clinical

observation, preferably assisted by the results of sensitivity tests, will allow for the early recognition of sulfadiazine resistance and the introduction of a more effective agent into the therapeutic regimen.

Chloramphenicol was substituted for sulfadiazine in the study because the latter had obviously lost its effectiveness and the organisms were uniformly sensitive to chloramphenicol. It is interesting to note that, although no resistant organisms developed, persistent carrier states or bacteriologic relapses appeared to be as frequent after chloramphenicol therapy as after sulfadiazine. Since this study was not designed to evaluate the use of chloramphenicol, no conclusions regarding its relative effectiveness can be drawn.

Summary

1. An outbreak of shigellosis due to Shigella sonnei Form I in an institutional population being routinely cultured is presented.

2. The appearance, persistence, and spread of sulfadiazine-resistant strains was demonstrated.

3. The therapeutic implications of the appearance of resistance strains is briefly discussed.

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Progress in Pediatrics

German Measles and German Measles in Pregnancy

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For 15 years German measles has been known to hold serious risks for the human embryo if contracted by the expectant mother during pregnancy. Yet, little progress has been made toward control of the disease. Furthermore, no firm epidemiologic observations have been collected to confirm the clinical evidence—although this is convincing enough. Much of the epidemiologic difficulty lies in case finding, which is no simple matter when the problem concerns members of society who will not even be born for several months after a mother's infection and who will have no rash or telltale sign that means rubella and only rubella.

Appreciation of the hazard came from clinical observations in Australia, where Gregg and others showed that an epidemic of rubella in 1939 and 1940 left in its wake a whole train of pathologic consequences for unborn babies: congenital cataract, deafness, mental retardation, and heart disease. American and European reports shortly confirmed this observation.

Although the first Australian observations definitely established that infection of a mother with the virus of German measles in the first trimester of pregnancy frequently proves teratogenic for the unborn baby, they did not quantitate these risks numerically. Did the babies of all infected mothers run into trouble or only a small percentage? No one knew because the data were assembled retrospectively with case finding based on pregnancies productive of defective babies. To evaluate risks it is necessary to know the normal as well as abnormal outcomes of pregnancies complicated by rubella.

Little by little, follow-up observations have been accumulated to confirm that the risk of gross deformity is indeed greatest during the first few months of pregnancy, and today the outlook for babies born after rubella-complicated pregnancies can be expressed percentagewise, as shown in the Table. The primary factor in judging the validity of this experience is, of course, reliability of the diagnosis of German measles. A physician's opinion was needed on this point. A next essential was to know when in pregnancy the mother had her infection. Both facts were decided before the baby was born, after which the mother was followed through to term when the impact, if any, upon the baby was observed. Only in this way—when the physician had made a definite diagnosis in the mother but did not yet know what the effect would be on the conceptus—could unbiased data be assembled by which to compute the risks of infection.

Today a follow-up report can be given on 100 pregnancies complicated by rubella and followed to term after the infection had been reported. Over 20% of first trimester infections produced either death or congenital defect—there is no way of predicting which—of the fetus. Second trimester infection, especially about the fourth month, appears to present a comparable hazard. The

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Outcomes of Rubella-Complicated Pregnancies by Trimester of Infection

Source of Data	1st Trimester			2nd Trimester			3rd Trimester			Total
	Total Births	Still-births	Congenital Defects	Total Births	Still-births	Congenital Defects	Total Births	Still-births	Congenital Defects	
Grövall & Selander[1]	13	2	0	13	1	1	2	0	0	28
Aycock & Ingalls[3]	2	0	1	1	0	0	0	0	0	4
Fox & Bortin[5]	9	1	1	1	0	0	2	0	0	12
Hill & Galloway[6]	5	0	1	2	0	0	2	0	0	9
Ingalls & Purshottam[8]	13	0	1	6	1	1	0	0	0	19
D. L. Brawner[7]	11	1	4	4	0	2	2	0	0	17
Personal	10	0	2	1	0	0	0	0	0	12
Total	63	4	10	28	2	4	9	0	0	100
%		6.3%	15.9%		7.1%	14.3%		0	0	

term congenital anomalies as used here includes only the unequivocal gross defects such as brachycephaly, mental retardation, and Mongolism, deafness, cataract, hypospadias, cleft palate, and hydrocephalus. For evident reasons controls were not assembled by clinicians originally reporting. Significance can be shown by relation of the kind of anomaly observed to the stage of pregnancy reached when the mother contracts the disease.[9]

The need now is to reexamine the behavior of rubella itself, to look for evidence of its epidemiologic impact on the unborn population—especially in the big rubella years—and to devise tangible preventive measures.

Cases of rubella reported to the State Department of Health (Fig. 1) in Massachusetts since 1917 are indicative of long-term fluctuations of spread in addition to the well-known seasonal variations. Something that approximates a seven-year rhythm is discernible with about three of the annual cycles often approaching a peak and the next few usually receding from it; three of the four largest outbreaks occurred during times of war.

Long-term behavior doubtless is determined in part by the relatively long incubation period, but a more decisive factor would seem to be a lower order of infectivity than for measles or mumps, which is revealed in the motor car-airplane era (Fig. 2). At least, the differing experiences of inductees in World Wars I and II point to an increasing speed of transmission of measles and mumps but not of rubella in the past 25 years. These infections were much more of a military problem in the slower times of World War I, whereas rates for rubella were actually higher (almost 10 per 1000 per annum) among inductees in the 1940's than in 1917-1918. The morbidity from German measles was, of course, inconsequential, clinically speaking, for these young men. The threat was for their wives or, more precisely, for the babies which the wives might bear if they happened to be in the early stages of pregnancy when contracting rubella.

No comparable observations on the incidence of German measles in young women of reproductive age are readily available. However, an appraisal has recently been made in the Department of Epidemiology of the Harvard School of Public Health of maternal-fetal experience with rubella in

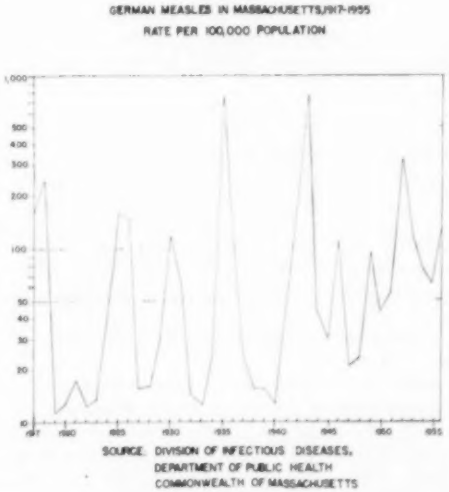


Figure 1

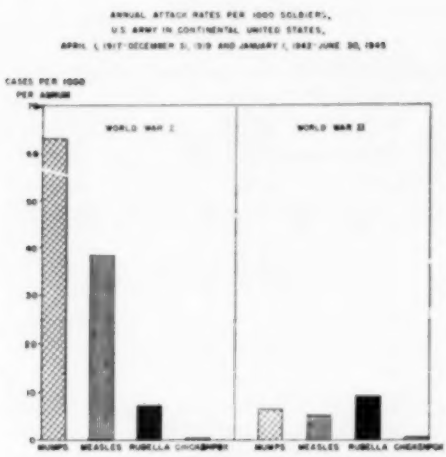


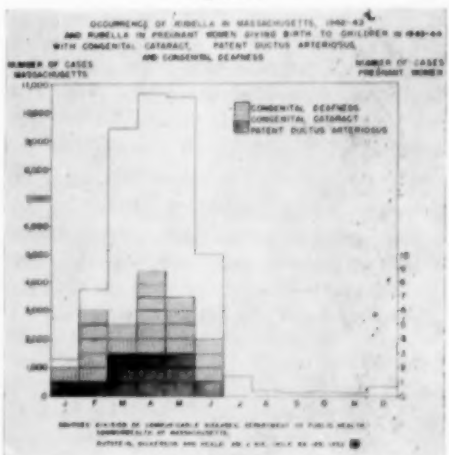
Figure 2

1942-1943, as measured by the births of defective babies a year later, in 1943 and 1944 (Fig. 3). The lowest block of shaded rectangles represents cases of patent ductus arteriosus—13 of the 26 cases of congenital heart disease previously reported by Rutstein, Nickerson, and Heald.[10] Above this is a block of 13 cases of congenital cataract discovered through the records of the Massachusetts Division for the Blind and the Massachusetts Eye and Ear Infirmary, and above that 10 patients with congenital deafness who were born after their mothers had rubella.[11] These children were located by search of the records of two of the five state schools for the deaf. Although many of those represented in the figure had more than one defect, each case is listed only in the index category and no case has been listed twice.

Rutstein and his colleagues had already shown a correlation of birthdays with the rubella season for children with patent ductus arteriosus admitted to the Children's Hospital. The present approach has assembled children with one or the other of three major congenital defects whose mothers while pregnant had had rubella either in 1942 or 1943. Patients with patent ductus arteriosus, congenital cataract, or deafness were arranged initially by month of birth; then the whole block was shifted en masse seven months to the left—that is to say, 7 months earlier in 1943 or back to 1942 as the case may be. The result is to arrange cases by gestational age. Infants shown were approximately 2 months old in utero. When this was done a wellnigh perfect correlation emerged between the specified defects and the two epidemics of rubella in the first half of the years 1942 and 1943. It is evident that the list is no more complete for defects than it is for reported cases of rubella, also shown on the chart. The data do, however, point clearly to a mass impact of rubella on unborn babies in those first two years of World War II. The epidemiologic findings are in harmony with conclusions heretofore based on clinical data.

It is hardly necessary to express significance mathematically for it is most unlikely for all events of the kind described to occur in the first half of the year merely from chance. When the over-all phenomenon is viewed against the Australian observations of the beginning war years, 1939 and 1940, it is clear that the epidemic counterparts occurred in the United States about two years later, after this country had entered hostilities. These were years when transmission of rubella would have been accelerated by

Figure 3



military furloughs and family movement incident to the training programs of war.

The findings indicate that inability to measure the impact of rubella on the embryo epidemiologically has been due to technical difficulties in case finding and lack of reporting. Demonstration of teratogenicity has therefore been limited to clinical evidence. The time has now come when the question of the teratogenicity of rubella is a finished chapter. The objective of the future is to anticipate and prevent the consequences of maternal infection rather than to cope belatedly with them by the use of gamma globulin or other measures.

The next move would seem to be squarely up to the virologist. The challenge is to "capture" the virus so that it can be dispensed much as vaccinia is dispensed. A practical step would be to allow women who have not contracted rubella in childhood to become actively immunized before marriage or pregnancy—especially in times of epidemic. It seems neither necessary nor feasible to entertain an elaborate plan of immunization by vaccine injections comparable to that used against poliomyelitis. Although that is conceivable, the simpler method would be for susceptibles to have the disease either naturally or artificially. Meanwhile pediatricians, physicians, and school nurses should encourage the acceptance of naturally developing rubella and the resulting immunity with the same seriousness with which they urge immunization against tetanus. Until the adult population is more highly immune than at present there is a slight risk that school children will bring the artificially acquired infection home to a susceptible and pregnant mother. On the other hand, the circumstances of infection could be adjusted intelligently, and there is every reason to believe that the gains would quickly outdistance the losses. At present the decision is simply going by default to nature.

The rationale of acting more vigorously in an epidemic year is the rationale of vaccinating during an epidemic of smallpox, although with German measles the risk is for the unborn, not the born. The consequences of rubella are, statistically speaking, negligible in children and adults; they are large and often tragic for the embryo.

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Case Reports

Syndrome of Congenital Hemihypertrophy and Elevated Urinary Gonadotropins

Occurrence in a Seven-Year-Old Boy

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Minor differences in size between the two sides of the body are common and usually have no significance. However, severe disproportion is relatively rare and there are less than 130 cases reported in the literature. In 1953 Silver and co-workers [1] described a syndrome of congenital hemihypertrophy and elevated excretion of urinary gonadotropins in two children who failed to show any other evidence of apparent endocrine disturbance. The purpose of this paper is to present the third case of this syndrome in a 7-year-old boy.

Report of Case

A boy was first seen in the New Haven Hospital Pediatric Out-Patient Clinic at the age of 10 weeks because of a difference in size of his legs. He had been born at term following an entirely uneventful pregnancy and had been delivered by Caesarian section. Birth weight was 3100 gm. (6 lb. 12½ oz.). Because he was cyanotic at birth, he had been given supplemental oxygen and after 24 hours appeared entirely normal.

When he was about 2 months old his mother first noted a difference in the size of his legs and brought him to the clinic. On physical examination the only positive findings were a diffuse enlargement of the left buttock, leg, and foot, the presence of a small café-au-lait spot on the left lower back and two small capillary hemangiomas on the right upper lid and the glabella. Both arms appeared to be equal in size.

At the age of 10 months he was admitted to the New Haven Hospital for diagnostic studies to determine the cause of the enlargement of the left leg. At that time the left leg measured 2 cm. longer than the right, the left foot 1 cm. longer than the right, and the circumference of the left thigh 2.5 cm. greater than the right. He did not use the enlarged limb as actively as the other but muscular power seemed to be equal in both. No difference in temperature or color of the legs was noted. Femoral pulsations were strong and equal, and no bruit was heard. Roentgenograms of the lower extremities revealed diffuse enlargement of the bones and soft tissues on the left, but these structures were otherwise normal.

At operation oxygen saturation was found to be the same in blood obtained from both femoral veins. Exploration of the subcutaneous tissue of the left leg revealed apparently normal blood vessels and lymphatics. No arteriovenous aneurysm was demonstrated. A biopsy of skin and subcutaneous tissue was interpreted as showing normal skin with slight edema of the subcutaneous tissue.

The patient was next seen in the Out-Patient Clinic at the age of 7 10/12 years. His mother reported that he had grown and developed normally. He had full use of his legs and was able to walk, run, and hop in a normal manner even when wearing regular shoes. Review of systems was not contributory. He weighed 24.5 kg. (54 lb.) and was 122 cm. (48 in.) tall. The capillary hemangiomas on the right upper lid and the brow were no longer visible. The café-au-lait spot on the left lower back measured 2.7 by 1.4 cm. It had an irregular border, and four 1 mm. darker brown areas

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Measurements

	Left	Right
Leg (ant. sup. spine to lat. malleolus)	63 cm.	61 cm.
Leg (med. condyle of tibia to med. malleolus)	28.2 cm.	27.0 cm.
Leg (circumference of thigh)	36.0 cm.	30.0 cm.
Leg (circumference of calf)	19.0 cm.	15.5 cm.
Length of femur (by roentgenogram)	35.7 cm.	34.0 cm.
Length of tibia (by roentgenogram)	28.5 cm.	26.5 cm.
Arm (lateral epicondyle to styloid)	28.3 cm.	27.0 cm.
"Bone age"	6 yr.	5½ yr.

were scattered over its surface. The skull was symmetrical with a circumference of 52.5 cm. (20⅔ in.). The tonsils were hypertrophied but equal in size. Twelve permanent teeth had erupted (eight incisors and four front molars). The face, clavicles, chest, and back were symmetrical. Both testes and the penis were of normal size. The little fingers of both hands were short, the left extending just proximal to the distal crease of the ring finger and the right little finger extending only to within 0.5 cm. of the distal crease of the ring finger on that hand. Neither little finger showed any unusual incurving. Radial, femoral, and dorsalis pedis pulses were all strong and equal bilaterally. His nails and hair were entirely normal.

Requestioning the mother disclosed that the patient's four brothers who were 2, 3, 5, and 6 years older than he were all in good health, although the 11-year-old sibling was said to be "short for his age." No asymmetry was present in any member of the family. Both parents were of normal height. The mother also had a café-au-lait spot on her lower back.

Routine blood count and urinalysis were normal. A 24-hour urine sample was collected and assayed for gonadotropins. It was positive for 35.2 mouse uterine units and negative for 70.4 mouse uterine units per 24 hours of urine.

Comment

Although only a relatively few cases of hemihypertrophy have been described in the medical literature, it is probably not a rare condition. Most cases are not reported because the hemihypertrophy occurs as an isolated finding and no definite etiology can be ascribed that will satisfactorily explain the pathogenesis of the abnormality. Among the mechanisms that have been incriminated as possibly causing the condition are embryonic variants [2] (incomplete twinning),[3,4] embryonic defects of the vegetative nervous system,[5] arteriovenous aneurysms,[3,5,6] nevi, telangiectasis, neurofibromatosis,[7,8] abnormalities of the lymphatic system,[3,9,10] lesions of the brain,[5,11] heredity,[12-14] congenital syphilis,[3] endocrine factors,[5,15-18] and mechanical influences. Silver and his coauthors [1] suggested that the condition might be a variant of ovarian agenesis (now more correctly termed gonadal dysgenesis) where congenital abnormalities (including disproportion of various parts of the body) and elevated levels of urinary gonadotropins may be part of the clinical picture.[19-23]

Ward and Lerner [24] have made a comprehensive review of the subject of congenital hemihypertrophy, and they noted that other abnormalities had occurred in approximately 50% of the reported cases. These included nevi,[4,13,25,26] pigmentation of the skin,[27] telangiectasis,[28] abnormal nail growth,[13] premature eruption of teeth,[13] excessive secretion of sebaceous and sweat glands,[13,29] thickening of the hair on the involved side,[3,29,31] syndactylism,[3] polydactylism,[25] clubbed feet,[13] enlargement of the tonsil,[28] hypospadias,[25] cryptorchidism,[25] supernumary nipples,[32] congenital heart disease,[25] and hypertrophy of one of the pair organs on the involved side.[17] In addition to these findings Silver and co-workers called attention to the unusual small size of their patients at birth after a reportedly normal gestation, persistence of shortness of stature, a difference in the maturation of epiphyseal centers ("bone age") on the two sides of the body and incurving of the little fingers.

An association between hemihypertrophy and a disturbance of endocrine function has been noted. It has been reported as occurring with the adrenogenital syndrome [16-18] and in two of these cases [16,18] virilism resulted from an adrenogenital tumor. In one [18] a Wilm's tumor (embryoma) of the kidney subsequently developed. Björklund [33] has reported two additional cases of hemihypertrophy in whom Wilms' tumors subsequently developed.

Russell [34] has recently described disproportion in the two sides of the body in two patients with shortness of stature, small size

at birth, and incurved little fingers. He also called attention to the peculiar mouths of his patients in whom the outer angles are drawn down, producing an inverted "V" or "shark-mouth." These findings in Russell's patients would appear to be identical to those previously reported by Silver and co-authors. Unfortunately assays for urinary gonadotropins were not performed in Russell's patients.

The boy herein reported had moderate disproportion between the extremities on the two sides of his body and a marked and abnormal elevation in the excretion of urinary gonadotropins. At the age of 7 10/12 years his excretion of urinary gonadotropins was more than 35.2 but less than 70.4 mouse uterine units per 24 hours. In our laboratory normal women during the reproductive period of life have been found to excrete more than 6.5 and less than 52 mouse uterine units and all normal children under 8 years of age have been found to excrete less than 2 mouse uterine units per 24 hours.

The only other findings of note in our patient were a 4 cm. café-au-lait spot over the right lower back, shortening of both little fingers, and moderately retarded maturation of epiphyseal centers ("bone age"). There was a difference in bone age between the two sides of the body. No evidence of any endocrine disturbance, vascular abnormality, or defect of the nervous system was noted.

Russell [3,4] has suggested that the abnormalities occurring in his two patients (and in three others with similar findings but in whom differences in the two sides of the body were not present) were due to environmental influences causing an acquired intrauterine growth-failure which probably affected the fetus during the sixth and seventh intrauterine week. In our patient pregnancy had been normal as far as could be determined, and in the other two cases of this syndrome [1] gestation had been entirely uneventful at least until the seventh month, when the mother of one of the previously reported patients had been in a minor automobile accident after which time she had experienced no further gain in weight until the delivery of the child.

Several of the cases of hemihypertrophy have been associated with cryptorchidism and hypospadias. This suggests that the underlying disturbance in fetal development may occur at the time that the sexual apparatus is being differentiated. A similar mechanism has been proposed as occurring in gonadal dysgenesis. In this condition it has been found that the majority of cases have a chromosomal pattern that is characteristic of males, even though the patients may have the outward appearance of immature females. It would be of interest to have studies of the chromosomal pattern of various cells in apparent girls with hemihypertrophy, since this might be an aid in determining the "basic" sex of the person.

Summary

The third case of the syndrome of congenital hemihypertrophy and elevated urinary gonadotropins is reported in a 7-year-old boy.

The only other abnormalities of note were a café-au-lait spot on his back, shortening of both little fingers, and moderately retarded maturation of epiphyseal centers ("bone age"). There was a difference in bone age between the two sides of the body.

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Mild Neonatal Toxoplasmosis

Case Report with a Four-Year Serologic and Dermal Sensitivity Study

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Congenital toxoplasmosis is a generalized infectious disease in humans and animals caused by the protozoan, Toxoplasma gondii, which is transmitted transplacentally from the mother to the fetus. Signs of the disease may become apparent in utero or within a few days, weeks, or months after birth. That human congenital Toxoplasma infections may be mild or asymptomatic as well as severe and fatal is not well known. Most of the congenital toxoplasmosis cases reported in the literature have been severe or fatal infections either with clinical signs of central nervous system damage, such as chorioretinitis, psychomotor retardation or disturbances, cerebral calcifications, and hydro- or microcephaly, or visceral manifestations of jaundice and hepatosplenomegaly or any combination of the above.[1] A definite diagnosis can be established by adequate serologic tests[2,3] or by demonstrating the parasite in body fluids or tissues. The following case of congenital toxoplasmosis is considered of value because it deals with a relatively mild acute neonatal infection which was diagnosed and followed by serial serologic tests for four years in the absence of classical clinical signs.

Report of a Case

The patient was born at the New York Hospital on July 15, 1951. His mother, 28, father, 37, and a 4-year-old sibling are living and well. The father had malaria in 1943 and has hay fever. There are no known cases of tuberculosis, syphilis, epilepsy, cancer, or other familial diseases in the family.

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The mother, who is para 2, gravida 2, Rh-positive, and Mazzini negative, felt well during her pregnancy except for two periods: once during her fourth month when she felt exceedingly tired for one week due to a condition diagnosed as the grippe without fever, and during the seventh to ninth months of her pregnancy when she rested in bed most of the time to relieve painful spasms in her right calf, which were aggravated in the upright position. No other complications of pregnancy were detected.

This baby boy weighed 3500 gm. on July 15, 1951, following a full-term spontaneous delivery under meperidine (Demerol) hydrochloride and light ether anesthesia. He had some initial respiratory irregularity and cyanosis which were relieved completely by pharyngeal aspirations and oxygen. During the first two days of life he behaved normally. On July 17 he had one episode of projectile vomiting, followed by occasional regurgitation of small amounts at subsequent feedings. The infant did not appear ill, and examination was negative except for a mild pharyngitis. On July 19 there was no further vomiting, but he was irritable and lethargic and his daily morning temperature for the first time was elevated to 101.3 F (38.5 C), despite an adequate formula intake and normal stools. Examination revealed no definite cause for the illness. The blood count and urinalysis were normal on that date. On July 20 the temperature rose to 102.7 F (39.3 C) and the baby was transferred from the maternity to the pediatric service.

Physical examination revealed a well-developed, well-nourished 5-day-old white infant alternately somnolent and irritable. His measurements were as follows: temperature, 100.9 F (38.3 C); weight, 3350 gm.; length, 50 cm.; head, 34.5 cm., and chest, 32.5 cm. His skin turgor and color were good. No jaundice, bleeding tendencies, or twitchings were evident. The anterior fontanelle measured 4 cm.×3 cm. and was not tense. The pupils were round, equal, and reacted to light. The fundi appeared normal. The pharynx was mildly injected, and a small punched-out ulcer with a gray base 2-3 mm. in diameter was present on the left side of the soft palate. The neck was supple. The liver was palpable 2 cm. below the

TABLE 1.—*Spinal Fluid Analyses*

Date	Color	Pressure	Cells	Culture	Smear	Protein	Sugar
7/22	Clear	Not increased	5 WBC	No growth	No organism	77 mg.	61 mg.
7/26	Clear	Not increased	2 WBC	No growth	No organism	67 mg.	71 mg.
8/7*	Clear	Not increased	3 WBC	No growth	No orgabism	63 mg.	

* This spinal fluid was inoculated into mice, from which no parasites or organisms were subsequently recovered.

costal margin. The spleen was not felt. The remainder of the examination was not remarkable.

The following laboratory procedures were done in an effort to determine the cause of the daily low-grade fever which fluctuated between 96.8 F-102.7 F (36 C-39.3 C) from July 19 to July 31. Urinalysis: repeatedly normal. Blood counts: the Hgb. of 24 gm. on admission dropped to 17.4 gm. on discharge; the RBC dropped from 6,700,000 to 4,800,000 per cu. mm., while the WBC fluctuated between 10,000 and 16,300 per cu. mm. The differential, which on admission was 44% segmentals, 32% bands, 14% lymphocytes, 8% monocytes, 0 eosinophils, and 2% basophils, gradually changed and just prior to discharge was 18% segmentals, 13% bands, 63% lymphocytes, 13% monocytes, 3% Türk cells, and one nucleated RBC per 100 WBC. Throat culture: July 20, nonhemolytic Streptococcus, Staphlococcus aureus, Staphlococcus albus, and Micrococcus catarrhalis. Blood cultures: On July 20, 22, and 26 these were sterile. Urine culture: On July 20 showed no growth.

Spinal fluids were analyzed and results are

X-rays: July 23, chest and abdomen were normal. July 25, skull was normal.

Blood chemistries: July 24, BUN 17 mg.; CO_2 17.5 mEq/liter; chlorides 112 mEq/liter; calcium 8.5 mg.; sodium 151.2 mEq/liter; potassium 6.4 mEq/liter.

Bleeding time: July 25, one minute; coagulation time: 15 minutes (Lee-White).

Stool: July 27, culture was negative for Salmonella and Shigella; guaiac was negative; few pus cells were seen.

Circulating eosinophiles: Aug. 7, 192 per cu. mm.

On July 24 a clear vesicle 3-5 cm. in diameter on a thin erythematous base appeared on the right external nares and right nipple area. Adjoining these, many closely set discrete and confluent small vesicles developed forming clusters 10-20 mm. in diameter. Similar lesions appeared during the next five days on the left external nares, right cheek, periumbilical area, and left ring finger (Figure). On about the third day the lesions became necrotic in the center and gradually formed brown crusts which fell off 10-18 days later, leaving on one area near the right nipple a superficial pitted scar 7 mm. in diameter. Culture of the clear vesicular fluid aspirated on July 25 gave no growth. Smear of opaque material aspirated on July 28 showed only mononuclear cells in various stages of breakdown and no organisms. The dermatological consultant, Dr. Arthur Grace, on July 28 could not associate the lesion with any specific etiologic agent.

A blood sample, taken from the infant on July 25, contained dye test antibodies for toxoplasmosis in a dilution of 1:256 and complement fixing antibodies in a titer of 1:16. A repeat sample on July 31 showed the titer of dye test antibodies to have increased to 1:612 and the complement fixing antibody titer unchanged. A blood sample from the mother showed dye test antibodies present in a dilution of 1:612 and complement fixing antibodies in a dilution of 1:32. Sera from the father and 3-year-old sibling were negative. A tentative diagnosis of congenital toxoplasmosis was made on the basis of these serologic tests despite the absence of classical clinical signs.

Therapy consisted of the following: From July 20 through July 23 penicillin, 300,000 units daily,

The vesicular-crusted lesions on the external nares, cheek and anterior chest wall eight days after the onset of the rash.

was administered intramuscularly in divided doses. From July 22 to July 26 chloramphenicol (Chloromycetin) was given by gavage in divided daily doses of 100 mg. per kilogram for the first 24 hours followed by 75 mg. per kilogram for the succeeding 24 hours. It was discontinued because it had no effect on the fever and because diarrhea and regurgitation developed. However, the pharyngitis cleared within several days. When a tentative diagnosis of toxoplasmosis was made on July 27, sulfadiazine was started in dosage of 0.1 gm. per kilogram per 24 hours subcutaneously in divided doses for 3 days, followed orally by 0.2 gm. per kilogram per 24 hours in divided doses for 5 days, and then smaller doses for a total of 4 weeks. The blood sulfadiazine level was checked periodically: July 31, 7.4 mg. per 100 cc.; Aug. 2, 13 mg. per 100 cc., and Aug. 6, 11.3 mg. per 100 cc. High titer convalescent toxoplasma serum* in 4 ml. doses was administered intramuscularly on four successive days starting on July 30.

The infant's temperature became normal on July 31, after which he gradually improved. On Aug. 5, for the first time, the spleen was felt 1 cm. below the costal margin. Two ophthalmoscopic examinations were entirely normal. The patient was discharged in good condition on Aug. 8, 1951, weighing 3520 gm.

At home the infant's mental and physical development has been uneventful and normal up to the present age of 5 years. He walked without support at 15½ months. At 23 months he had a vocabulary of 50 words, spoke several two-word phrases, and was completely trained for bowel and bladder functions. The spleen was palpable until 3 months of age. At 4 months of age x-ray of his skull in multiple projections showed no evidence of intracranial calcifications. Between 5 and 20 months of age the infant had 5 recurrent typical herpes simplex lesions on his cheek and nose. Repeated ophthalmoscopic examinations following mydriatics during the first year and at 2 years revealed no fundus pathology.

* The serum, which was obtained from Dr. Heinz Eichenwald, had a dye test titer of 1:10,000 following a recent infection.

Serial toxoplasma antibody estimations were done on the sera of the patient and mother when the child was 4 months, 12 months, 2 years, 3½ years, and 4 years. The comparative results are listed in Table 2.

A toxoplasmic skin test and control were done on the child and mother when the child was 4 years old. Just prior to the skin test a blood sample was taken for antibody titer. Erythema without whealing was present at the skin test and control areas in 15 minutes in mother and child. After 48 hours there was no reaction at the site of the skin and control tests in the child, while a 3×3 cm. area of redness and induration appeared only at the site of the skin test in the mother (Table 2).

Comment

The persistent slight spinal-fluid-protein elevation and the prolonged fever which did not respond to antibiotics focused suspicion on a possible inflammatory or hemorrhagic disorder of the central nervous system. The significance of the elevated Toxoplasma dye test and complement fixing antibodies in the sera of the mother and infant was evaluated by serial serologic antibody determinations. Elevated antibody levels in sera of newborns tend to disappear after three to four months when due to transplacental transfer from the mother, while those due to active disease in the infant either persist or increase. In this infant there developed a fourfold increase of the Toxoplasma dye test antibody titer at 4 months followed by a gradual and complete disappearance of this antibody over a 3-year period. This left no doubt that this illness was an encephalitic manifestation of an active congenital Toxoplasma infection.

TABLE 2.—*Toxoplasmic Antibody Titers* and Skin Test*

	Child			Mother		
Age	Dye Test Antibodies	Complement Fixing Antibodies	Skin Test	Dye Test Antibodies	Complement Fixing Antibodies	Skin Test
10 days	1:256	1:16		1:612	1:32	
16 days	1:612	1:16				
4 mo.	1:1224	1:32		1:1224	1:16	
12 mo.	1:128	1:8		1:612	1:4	
2 yr.	Undiluted			1:64		
3½ yr.	0			1:16		
4 yr.	0	0	Negative	1:64	0	Positive

* The antibody titrations were determined during the neonatal period, at 4 months, 12 months, and 4 years by Dr. Heinz F. Eichenwald; at 2 years and 3½ years by Dr. Harry A. Feldman.

The mother probably developed an inapparent infection during her pregnancy. A search for the source of the mother's infection was unsuccessful. Blood obtained from a dog with whom the mother was in contact during her pregnancy revealed no Toxoplasma antibodies. Also, the father and sibling had no serologic evidence of infection. Transmission of the mother's infection to the infant probably occurred at the end of her pregnancy, because symptoms of the infant's acute illness appeared a few days after birth and because of the relative mildness of the infant's infection, as indicated by the absence of gross clinical signs. The mildness of the infant's infection might be attributed to the transplacental transfer of maternal antibodies which occurs during the last trimester of pregnancy, as well as such factors as a strain of low virulence or small number of invading parasites.

The scattered vesicular and crusted lesions present from the 5th to 23d day of illness were unusual and probably the result of a cutaneous hypersensitivity to Toxoplasma antigen. The usual type of rash reported in congenital toxoplasmosis is petecheal and purpuric, while the skin lesion described in acquired cases has been maculopapular.

Even though eosinophilia has been reported in toxoplasmosis, it was not present in this case.

That sulfadiazine and convalescent hyperimmune Toxoplasma serum helped control the infant's infection is suggestive. The dye test antibodies which persisted in the mother's serum for at least four years disappeared from the infant by three years. This is sooner than that observed by Eichenwald [4] in any of 60 patients with congenital toxoplasmosis, who were followed annually with serologic tests until at least 7 years of age. Only three of these children lost their dye test antibodies, two at 5 years and one at 7 years. Also, it has been demonstrated that sulfadiazine and antiserum will control proliferation of Toxoplasma in experimentally infected animals but will not usually rid the host of the parasites.[5]

The toxoplasmic skin test (delayed tuberculin type), which was performed on the mother and child when the latter was 4 years old, reflected the state of humoral immunity in each. After 48 hours the skin test evoked no reaction in the child, whose serum showed no demonstrable antibody, while a 3×3 cm. area of redness and induration developed at the site of the skin test in the mother whose serum contained dye test antibody. Although a high correlation has been demonstrated between dermal hypersensitivity and the presence of antibody,[6] a negative skin test has been reported both in persons with Toxoplasma antibody as well as in those with proved congenital toxoplasmosis.[1]

In view of the normal physical and mental development of this child up to the present age of 4 years, the prognosis appears to be very good.

This case might be considered atypical because it was relatively mild and free of the serious clinical signs associated with the acute congenital form of the disease. In a series of 130 cases of congenital toxoplasmosis, Eichenwald [4] found mental retardation in 75%, chorioretinitis in 60%, convulsions in 50%, and cerebral calcifications in 30%. Similarly, Feldman [7] in a study of 103 cases of congenital toxoplasmosis, found an incidence of chorioretinitis in 99%, cerebral calcifications in 63%, psychomotor retardation in 56%, hydro- or microcephaly in 50%, and convulsive episodes in 50%. These figures mainly represent the incidence of clinical manifestations of the subacute and chronic forms of toxoplasmosis, rather than the early mild form observed in this patient.

Summary

A relatively mild acute encephalitis due to congenital toxoplasmosis is presented in a newborn infant manifesting fever and slightly increased spinal-fluid protein. An unusual vesicular-crusted rash was present

from the 5th to 23d day of illness. The classical clinical signs of the disease were absent. The tentative diagnosis which was made in the neonatal period by serologic tests, was confirmed subsequently by a progressive rise and fall of Toxoplasma dye test and complement fixing antibodies in the sera of the patient and mother over a four-year period. Demonstrable antibody disappeared from the child's serum three years after the onset of his illness. Toxoplasmic skin tests made when the child was 4 years old evoked no reaction in the child but did produce a dermal sensitivity reaction in the mother whose serum still contained antibody. The physical and mental development of the child is normal up to the present age of 5 years. Early treatment with sulfadiazine and convalescent Toxoplasma serum may have been of value.

Dr. Heinz F. Eichenwald assisted in the management of this patient.

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Correction

Through error, the Table cited in the article "Accidental Transanal Perforation of the Rectum" in the March issue (p. 257) was omitted. The following is the Table which should have been included.

Causes of Peritonitis in Infancy and Childhood *

Appendiceal rupture	70%
"Primary" infection	10%
Associated with intestinal obstruction	8%
Miscellaneous	7%
Post-traumatic	5%

* Based on survey of 270 cases of peritonitis in childhood 0-15 years of age seen at Milwaukee County and Milwaukee Children's Hospitals 1940-1955.

Abstracts from Current Literature

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Urinary Tract Infections Caused by Antibiotic-Resistant Coliform Bacilli. W. M. M. Kirby, D. O. Corpron, and D. C. Tanner.—p. 1.

* Prevention of Recurrent Attacks of Rheumatic Fever. B. L. Lendrum and Charlotte Kobrin.—p. 13.

The Role of Rehabilitation in a Program for Handicapped Children. H. M. Wallace, J. S. Tobis, R. S. Siffert, M. A. Losty, and C. H. Elledge.—p. 26.

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Use of Poliomyelitis Vaccine Under Epidemic Conditions. Capt. R. S. Poos and Neal Nathanson.—p. 85.

* Pathogenesis of Eosinophilic Pneumonitis (Loeffler's Syndrome). W. L. Epstein and A. M. Kligman.—p. 95.

Elements of a Rural Rheumatic Fever Program. H. A. Grubschmidt.—p. 102.

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* Hypothyroidism in the Adolescent. F. P. Heald, R. P. Masland, A. E. Renold, and J. R. Gallagher.—p. 161.

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* Accidental Chemical Poisonings in Children. Harold Jacabziner.—p. 454.

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* Diagnosis of Congenital Dysplasia of the Hip in the Newborn Infant. S. S. Coleman.—p. 548.

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Maternal Factors in Hypochromic Anemia of Infancy. C. W. Woodruff.—p. 659.

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Typhoid-Paratyphoid Vaccine with Chloramphenicol in Recurrences of Salmonellosis. Sister Agnus Therese Simpler, Sister Maria Corazon Jarmillo, and Sister Gilmary Simmons.—p. 881.

Meningoencephalitis in Infectious Mononucleosis. E. P. Frenkel, C. B. Shiver Jr., Perry Berg, and T. N. Caris.—p. 885.

Fatal Vaccinia Associated with Cortisone Therapy. Sidney Olansky, J. G. Smith, O. C. E. Hansen-Pruss.—p. 887.

Effect of Antigonadotrophic Serum on Recent Intrasplenic Ovarian Implants of Castrate Mice.—It has been found that tumors appear with consistent regularity in the laboratory rodent ovary when it is transplanted to the spleen of a castrate animal.

In the experiments here reported 158 mice were treated with either antigonadotrophic serum (produced in rabbits against sheep pituitary-gland extracts), sheep heart antiserum, normal rabbit serum, or saline at intervals of 1 to 30 days after an autoplastic ovarian transplant to the spleen. It was found that no sign of gonadotrophic stimulation was present in 78% of the implants from animals receiving antiserum, whereas some degree of gonadotrophic stimulation was present in 88% of the implants from animals receiving one of several control solutions or no treatment at all after implantation.

The data presented in the present report are regarded as lending additional confirmation to the concept that tumors arise in ovarian grafts to the spleen of castrate animals under the influence of excessive gonadotrophic secretion.

Anerobic Glycolysis of Human Prostatic Adenoma: In Vitro Inhibition by Estrogen and by Androgen and Estrogen.—The clinical usefulness of estrogens in treatment of carcinoma of the prostate scarcely needs documentation, but the mechanisms whereby the effects are produced are incompletely understood. The present study experimentally proves that the estrogens must have a direct local action on the prostate and that testosterone alone

is the most effective inhibitor. However, the dose required to obtain inhibitory levels would be of the order of 5 mg. per kilogram body weight intravenously.

Effects of Stress on Serum C^{14} Levels in Rats Following Administration of Hydrocortisone-4-C^{14} and Corticosterone-4-C^{14}.—One of the theories which has been proposed to explain the increased pituitary secretion of ACTH after the application of a stressful stimulus to the organism is the concept that the increased demand of the peripheral tissues for adrenocortical hormones during stress results in a lowering of the cortical hormone titer in the blood, thereby stimulating the pituitary to secrete increased quantities of ACTH.

In the experiments reported in this paper, C^{14}-labelled hydrocortisone and corticosterone were used in rats in an attempt to determine whether the application of such procedures as exercise or the injection of epinephrine or histamine altered (a) the half-life of the radioactive label in the blood or (b) the blood levels of the radioactive steroid when it was infused into the animals at a constant rate.

Although little, if any, positive evidence was found to substantiate the concept of increased peripheral utilization of adrenocortical hormones during stress, the evidence obtained from these experiments would seem to warrant a conclusion of "not proved" as regards this theory.

Parathyroid Function and the Plasma Citric Acid and Calcium Response to Nephrectomy.—The relation of calcium and citric acid metabolism has been the subject of numerous studies. However, it has remained a question as to whether or not there is a specific endocrine mechanism relating calcium and citric acid.

The results presented here demonstrate clearly that the parathyroid gland exerts an effect on the plasma calcium and citric acid response to nephrectomy.

Evidence is summarized pointing to an effect of parathyroid hormone on citric acid metabolism in the rat, rabbit, and guinea pig.

The Influence of Age on the Development of Adrenal-Regeneration Hypertension.—It has been shown that uninephrectomized rats given 1% sodium chloride to drink develop hypertension and widespread vascular disease following adrenal enucleation. The rise in blood pressure occurs as the adrenal cortex regenerates from the capsule and cortical cells adherent to the capsule which remains in situ after regeneration hypertension.

In the experiments here reported, by the end of eight weeks the immature rats had developed marked hypertension and arteriolar lesions of variable severity in the kidney, heart, brain, adrenal capsule, mesentery, pancreas, and submucosa of the gastrointestinal tract. The arteriolar lesions closely resemble the fibrinoid arteriolar necrosis of malignant hypertension in the human being.

In the same length of time the young mature rats, on the other hand, showed only a slight rise in blood pressure and fibrinoid vascular necrosis was entirely absent.

Since adrenal-degeneration hypertension and concomitant vascular disease develop in actively growing rats but not in older animals, it is suggested that growth hormone may play a significant role in the genesis of this form of experimental hypertension and vascular disease in the rat.

Interrelations Between Thyroxin and Adrenalin in the Regulation of Oxygen Consumption in the Albino Rat.—Thyroidectomy inhibited and thyroxin potentiated the calorigenic effect of Adrenalin.

The sensitivity to Adrenalin was so increased by thyroxin, that a dose of Adrenalin (100γ/100 gm. body weight) tolerable to intact or thyroidectomized animals was fatal to those animals receiving more than 3γ of thyroxin.

Prevention of Recurrent Attacks of Rheumatic Fever.—In reviewing the data obtained on 100 children who had had rheumatic fever the authors observed three disturbing facts concerning follow-up care: First, almost one-third of the children were no longer under medical supervision; secondly, two-thirds of these 100 children were not receiving prophylactic medication; thirdly, adjustment problems at school and home after leaving the convalescent home were not always dealt with properly. These observations led to a careful scrutiny of the data in an attempt to find out why these three situations occurred and how they could be prevented.

The authors conclude that the initiative of the patient and his parents does not suffice. Success in preventing recurrences depends on the development of a community-wide program, including some professional education and the dissemination of information about current rheumatic fever research.

Pathogenesis of Eosinophilic Pneumonitis (Loeffler's Syndrome).—It is the aim of the authors to present some notions on the pathogenesis of Loeffler's syndrome drawing upon experiences encountered in studies of the prophylaxis of poison-ivy dermatitis. In giving over 1000 subjects hyposensitizing of a synthetic chemical that is one of the allergens in poison ivy and related plants, eosinophilic pneumonitis developed in 7 patients. The pathogenesis of eosinophilic pneumonitis is constructed as follows: The initial event is an eosinophilia, often allergic but sometimes of other causes. The lungs, and less importantly other viscera, trap or filter out the eosinophiles in some unknown way. The histopathological alterations in the lungs are massive enough to be revealed by x-rays. The authors state these concepts require further experimental verification.

Hypothyroidism in the Adolescent.—Hypothyroidism in the adolescent differs from that in the adult in one important aspect. This difference is its effect on growth and development. Too often the obese adolescent is thought to be hypothyroid when actually there is no clinical or laboratory evidence to support the diagnosis. Clinically the diagnosis should be strongly suspected if one sees a retardation or a cessation of growth in a child whose growth had previously been progressing in an orderly fashion.

The various laboratory tests are discussed as to their significance in the diagnosis of hypothyroidism in the adolescent. The basal metabolic rate must be evaluated closely before great significance can be placed on it. The protein-bound iodine level, the measurement of the uptake of radioactive iodine (I^{131}) by the thyroid gland, and the evaluation of skeletal age by means of hand-wrist roentgenograms are reliable indices of thyroid function in a suspected hypothyroidism.

The authors present the findings of four adolescents with hypothyroidism and discuss the varied aspects of the condition in these patients.

Accidental Chemical Poisonings in Children.—The possibility of preventing accidental poisoning (by chemicals other than illuminating gas) was studied by analyzing 454 cases that occurred in children under the age of 16 in New York City in 1954. Of the total number, 84% occurred in persons in the age group 0-3 years. The high incidence in this age group is related to the child's exploratory nature coupled with inexperience and lack of caution. Drugs were responsible for 47% of all poisonings with aspirin as the chief offender and barbituates as the second leading cause in this category. Bleaches were the chief offenders of the household preparations.

Lead intoxication was observed most frequently in persons in the age group 1-3, cases in this group actually accounting for 87% of the total. A disproportionate number of accidents occurred in the poor socioeconomic areas and a striking difference was noted in incidence by race, with cases in nonwhites greatly predominating. Lack of adult supervision and disregard of elementary precautions were frequently observed.

The author suggests that the prevention of poisoning requires a team approach.

Diagnosis of Congenital Dysplasia of the Hip in the Newborn Infant.—The author stresses the importance of early diagnosis and treatment of congenital dysplasia of the hip in newborn infants. He proposes that if any one of the following conditions is found the diagnosis can be established: (1) lateral or posterolateral manual displaceability of the femoral head (jerk of exit), with an otherwise normal pelvic x-ray; (2) an acetabular index of 40 degrees or more without demonstrable displaceability of the hip; (3) lateral disposition of the femoral neck by x-ray examination, in the absence of demonstrable displaceability of the hip, and with or without an elevated acetabular index; (4) persistent and unequivocal limited abduction of the flexed thigh, with or without abnormal x-ray changes; (5) any combination of the above.

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The Maturation Factor in Enuresis. John Bostock and Marjorie G. Shackleton.—p. 1042.

Clinical Observations on Infections with Influenza and Coxsackie Viruses in North Queensland, 1953-1954.—In the latter part of the year 1953, influenza-like illness occurred in epidemic proportions in the area under study. Investigation of this epidemic lead to the isolation of two infective agents. The most commonly isolated was the virus influenza B. The other was a Coxsackie virus group B type 4. In the cases diagnosed as influenza B the average duration of fever was 5.2 days and common symptoms were cough and sore throat. Several patients, however, had no respiratory symptoms but did have fever and myalgia. The patients with Coxsackie group B virus had an average duration of fever of 4.7 days, and none had signs of aseptic meningitis which had previously been associated with this virus in many instances.

In 1954 a number of patients were studied during an epidemic and the influenza group A virus was isolated. No significant difference was noted between the clinical manifestations of

A or B influenza. The Coxsackie virus group A was isolated from only one patient during 1954, and it was felt by these investigators that it was probably unrelated to the patient's illness. Neutralizing antibodies to the specific infection were found in the patients studied and a rising titre was found in the convalescent period in most patients whether they were infected with the influenza or Coxsackie virus. A number of patients whose clinical features suggested that they belonged to the epidemics gave negative results to investigations for isolating the specific virus in antibody response to these viruses. The authors stress the difficulty in making a diagnosis unless virology studies can be accomplished.

Medizinische Klinik, Berlin

51, No. 28 (July 13) 1956

* Contribution to the Therapy of Morbus Boeck of the Lung. H. Bellers.—p. 1186.

51, No. 29 (July 20) 1956

* Incapacity of Separation of Letters and of Reading in Amblyopia Due to Strabismus. W. Ehrich.—p. 1236.

51, No. 30 (July 27) 1956

* Prednisone Therapy of Nephrosis in Childhood. F. K. Friederiszick and E. Hoffecker.—p. 1260.

Contribution to the Therapy of Morbus Boeck of the Lung.—The benefits of cortisone treatment of sarcoidosis of the lungs is discussed in an adult case.

Incapacity of Separation of Letters and of Reading in Amblyopia Due to Strabismus.—In cases of one-sided amblyopia due to strabismus, the letters arranged in a series fuse and reading difficulties exist. Various explanations are discussed. Special training methods have been devised.

Prednisone Therapy of Nephrosis in Childhood.—Eight children, 2 to 8½ years of age, with the diagnosis of "genuine lipoid nephrosis" received 20 to 30 mg. of prednisone daily by mouth divided into four doses, combined at first with an antibiotic, as a rule tetracycline. The diet was rich in calories and protein and poor in sodium chloride. Fruit and vegetables were given abundantly. All cases responded with a diuresis between the 5th and 10th day, with disappearance of edema. The serum cholesterol level decreased, the total protein level increased. The proteinuria decreased and ceased in three cases. In only one case, a boy 5 years of age, the improvement was transitory, the decrease of cholesterol and proteinuria was less marked, and the protein level of the blood decreased further. It was not possible to find a reason for this refractory result. In a couple of cases an upper respiratory tract infection produced a recurrence after about two and one-half to three months of well being. Both responded to the medication as used before. After dismissal from the hospital, prednisone was given in a daily dosage of 5 mg. for several months under maintenance of the diet. Three cases treated for four to six months became entirely free of any disturbance.

Metabolism, New York

5, No. 5 (Sept.) 1956

* The Influence of Vitamin Supplementation of the Diets of Pregnant and Lactating Women on the Intelligence of Their Offspring. R. F. Harrell, E. R. Woodyard, and A. I. Gates.—p. 555.

Studies in Disorders of Muscle: XI. The Problem of Pentosuria in Progressive Muscular Dystrophy. G. T. Perkoff and F. H. Tyler.—p. 563.

Bone Salt Metabolism in Human Rickets Studied with Radioactive Phosphorus. G. C. H. Bauer, A. Carlsson, and B. Lindquist.—p. 573.

A Comparative Study of Aldosterone and Desoxycorticosterone in Electrolyte and Water Excretion in an Addisonian Patient. A. F. Muller, E. Engel, A. Falbriard, and R. S. Mach.—p. 601.

The Influence of Vitamin Supplementation of the Diets of Pregnant and Lactating Women on the Intelligence of Their Offspring.—Dietary supplements were provided to 2400 women equally divided between a maternity clinic in Norfolk, Va., and Leslie County, Ky. Four tablets were used as follows: Tablet A, 200 mg. ascorbic acid; tablet B, 2 mg. thiamine, 4 mg. riboflavin, 20 mg. niacinamide, 15 mg. iron; tablet C, inert placebo; tablet D-2 mg. thiamine.

Eighty per cent of the Norfolk women were Negro and all were from low economic levels. Their diets were poor because of economic limitations. The women from rural Leslie Coun-

ty, on the other hand, were all white and their diets were "not conspicuously inadequate." Intelligence testing was done on the offspring at 3 years in both groups using a standard method. In the Norfolk group, intelligence was also tested at 4 years; 518 children were available for testing at age 3 and 370 at age 4 in Norfolk; 811 children were tested in Kentucky.

The mean intelligence of the children born in Norfolk was significantly higher in those whose mothers received supplements in the latter part of pregnancy than in those who received the placebo. This was most marked in the cases where the multivitamin preparation was administered. In the Kentucky study there was no significant difference between the groups receiving different tablets as regards mean level of intelligence. The suggestion is made that vitamin supplementation will raise the level of intelligence of the offspring of mothers whose diet is deficient in vitamin content.

Minerva pediatrica, Torino

8, No. 1, No. 2 (Jan. 14) 1956

* The Use of Methylandrostendiol in the Treatment of Premature Infants. M. Malaspina and P. Nicola.—p. 1.
* Ptosis of the Kidneys and the Ureters Following Extensive Paralysis Due to Poliomyelitis. S. Scarabicchi and A. Terragna.—p. 6.
The Absorption of Penicillin Administered by Rectum. A. Albanese.—p. 15.
A Clinical, Radiological and Histological Contribution to the Knowledge of Ganglioneuroma. R. De Luca, P. Barone, and G. Blandino.—p. 18.
Comments on Psychometric Findings in Children, Cured of Tuberculous Meningitis. A. Della Volte.—p. 31.

8, No. 3, No. 4 (Jan. 28) 1956

* The Anterior Pituitary Somatotrophic Hormone (STH) and Glucogone: Preliminary Studies on the Administration of STH in Von Gierke's Disease. R. Bulgarelli.—p. 37.
Streptomycin Diapneumotherapy in the Treatment of Bronchial and Pulmonary Complications of Pertussis. E. Egidi and M. Malaspina.—p. 45.
* The Treatment of Erythrodermia Desquamative (Leiner's Disease) by Vitamin B_{12} Given Orally. A. Nicolini.—p. 53.
The Renal Function of Children with Acute Rheumatic Fever with Arthritis and Receiving Cortisone Treatment. C. Cipolloni and A. Paci.—p. 57.
The Hormone-Salicylate Treatment of Rheumatic Disease in Children. G. Cernushi.—p. 66.

8, No. 5 (Feb. 4) 1956

Discussion Regarding the Treatment of Various Types of Tuberculosis in Children by Streptomycin-Isoniazid. M. Malaspina and A. Piccione.—p. 73.
* An Unusual Complication of Hiatus Diaphragmatic Hernia. A. Massarella and C. Pototschnig.—p. 84.
* Unusual Clinical Aspects of Rheumatic Disease. G. R. Mitolo and B. Dolcetta.—p. 89.
Infectious Hepatitis in Children. N. Pomponio and N. Pontorieri.—p. 102.
* Acrodynia and ACTH. C. Fracchia and G. Canestri.—p. 105.

8, No. 6 (Feb. 11) 1956

* Some Radiological Aspects of Mucoviscidosis, the Pulmonary Component of Cystic Fibrosis of the Pancreas. C. Zunin and C. Romano.—p. 117.
* The Urinary Elimination of the 17-Ketosteroids and of the 11-Oxycorticoids in Children with Congenital Heart Disease. M. Malaspina.—p. 125.
The Treatment of Scarlet Fever by Terramycin in Hospitalized Cases. M. Cristofani and F. Giannelli.—p. 130.
An Atypical Case of Q Fever with Localized Lymph Node Involvement. R. Morbidelli.—p. 134.
Subdural Hemotoma in Children. A. Morello and L. F. Levy.—p. 140.

8, No. 8 (Feb. 25) 1956

Congenital Malformations of the Digestive Tract of the Newborn. U. Vignolo-Lutati.—p. 187.
Some New Applications of Stratigraphy in Heart Cases in Children. L. Buffoni and G. Porro.—p. 191.
A Radiological Study of Hirschsprung's Disease. A. Limonta.—p. 194.
* The Production of Riboflavin "In Vitro" by Intestinal Bacteria. L. Bavastrelli and G. Russo.—p. 203.

The Use of Methylandrostendiol in the Treatment of Premature Infants.—Twenty premature infants were given by mouth, between feedings, methylandrostendiol, 2 to 3 mg. per kilogram per day, in an alcohol-glycerol medium, over periods of 30 to 45 days. Fourteen of the infants showed a definitely increased rate of gain in weight; the increase was from 17 to 24 gm. per day. There was no change in the rate of gain in three infants and a small decrease in the rate in three infants. After the first few days, the total protein and especially the gamma-globulin of the infants' sera were found to have increased in amount.

Ptosis of the Kidneys and the Ureters Following Extensive Paralysis Due to Poliomyelitis.—A definite ptosis of the kidneys was observed in 10 of 18 children, who had had extensive paralysis of the abdominal and lumbar muscles as a result of poliomyelitis. This condition was diagnosed following intravenous pyelography.

The Anterior Pituitary Somatotrophic Hormone (STH) and Glucogone: Preliminary Studies on the Administration of STH in Von Gierke's Disease.—The pituitary somatotrophic hormone has been reported as stimulating the alpha cells of the pancreas to secrete glucagone, which, in turn, will lead to the breakdown of glycogen. Thus its use in treating patients with von Gierke's disease would seem rational. Bulgarelli has tried this therapy with two patients; with one patient there was a definite but moderate rise in the blood sugar; no appreciable change was noted in the sugar metabolism of the second patient. He recommends its use in all cases of glycogen-storage disease, since it has growth-stimulating properties even when the glycogen storage difficulties may not always be overcome.

The Treatment of Erythrodermia Desquamativa (Leiner's Disease) by Vitamin B_{12} Given Orally.—Excellent results were obtained in the treatment of Leiner's Disease by daily doses of 50 μ gm. of vitamin B_{12}. Its possible value in some cases of atopic eczema is suggested.

An Unusual Complication of Hiatus Diaphragmatic Hernia.—The complication was the presence of an esophageal stenosis with a secondary enlargement of the upper esophagus. The condition was corrected by surgical procedure.

Unusual Clinical Aspects of Rheumatic Disease.—The authors stress that rheumatic fever attacks practically only the mesodermal tissues; since almost any of these tissues may be attacked, it is not surprising that an early diagnosis is not always made. Several such cases are reported.

Acrodynia and ACTH.—Four cases of acrodynia are reported. ACTH (20 mg. daily) proved efficacious in shortening the duration of the disease in the three cases in which it was used. No striking improvement had followed the use of the other drugs frequently recommended for this condition—Bellergal (belladonna, ergotamine, and barbiturates), vitamins B_1 and B_6, Priscol, or adenosinetriphosphoric acid.

Some Radiological Aspects of Mucoviscidosis, the Pulmonary Component of Cystic Fibrosis of the Pancreas.—Cystic fibrosis of the pancreas may occur in any of three types, two of which are incomplete and one complete. (a.) The respiratory manifestations may be present without apparent signs of pancreatic insufficiency. (b) The signs of pancreatic insufficiency may be present without any respiratory involvement. (c) Both respiratory and pancreatic manifestation may be present. The pulmonary signs have their onset with the secretion into the bronchi of a thick viscid mucous secretion; subsequently secondary bacterial involvement will usually appear, and frequently emphysema, atelectasis, and pneumothorax. The pulmonary signs may antedate steatorrhea by a considerable period of time. The appearance of loss of weight and steatorrhea will clinch the diagnosis.

The Urinary Elimination of the 17-Ketosteroids and of the 11-Oxycorticoids in Children with Congenital Heart Disease.—Twenty-four children with congenital heart disease, eighteen of them with cyanosis, showed a sub-normal secretion of the 17-ketosteroids and the 11-oxycorticoids in the urine; this would appear to indicate hypofunction of the adrenocortical glands. Five of the children were relieved of their cyanosis by surgery; 15 days later there was found to be a definitely increased excretion of these steroids.

The Production of Riboflavine "In Vitro" by Intestinal Bacteria.—It has been claimed that the success of Aureomycin therapy in the cases of children with diarrhea was due to a change in the intestinal flora, and especially to the destruction of certain bacteria which destroyed the vitamin riboflavin (B_2). The authors claim that they have refuted this thesis by certain "in vitro" experiments they have performed.

They found that cultures of Bacillus coli communis, Bacillus Dysenteriae Flexneri, and enterococci from the stools of children with diarrhea did produce riboflavin and not destroy it. Cultures of Proteus morgani and Proteus vulgaris, and prevailing fecal bacteria after Aureomycin therapy, did not produce riboflavin.

Monatsschrift für Kinderheilkunde, Berlin

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Opening Address: W. Keller.—p. 73.
Influenza and Other Virus Diseases of the Respiratory Tract ("Grippe"). R. Haas.—p. 76.
Virus Diseases of the Respiratory Tract Except "Grippe." H. Lippelt.—p. 84.
Diagnosis and Differential Diagnosis of Viral and Rickettsial Diseases of the Upper and Lower Respiratory Tract. W. D. Gerner. pp. 92-102.
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Differentiation of So-Called "Vomiting and Intestinal Grippe" from Influenza. G. A. v. Harnack.—p. 104.
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Pathogenetic Significance of Nasal Sinusitis in Childhood. P. Biesalski.—p. 107.
Rare Otogenic Complications in Early Infancy. H. Sandmann and H. Weiss.—p. 107.
Clinical Picture of Influenzal Sepsis with Meningitis in Infancy. H. U. Hoffmann.—p. 110.
A New, Stable Antigen for Complement and Skin Test in Toxoplasmosis. O. Thalhammer.—p. 110.
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Influence of Weather upon Diseases of Children. W. Menger.—p. 119.
Report on the Status of Active Immunization Against Poliomyelitis:
1. Report on the Salk Vaccine. O. Vivell.—p. 121.
2. Experiences with the German Polio Vaccine. W. Hennessen.—p. 128.
3. New Considerations Regarding Safety Testing of Polio Vaccine. O. Guenther.—p. 133.
Polio Antibody Studies in the Population and Its Practical Significance for Polio Vaccination. W. Keller.—p. 135.
Polio Antibodies in Certain Families in Geneva, Switzerland. R. Martin Du Pan.—p. 136.
Results of Polio Vaccination in the Children's Clinic of Wuerzburg. Bommer.—p. 138.
The Clinical Picture of Encephalitic Localization of Poliomyelitis. M. Hertl.—p. 142.
Disturbances in Acid-Base Balance: A Problem in the Treatment of Polio Patients with Respiratory Paralysis in the Respirator. W. Droese, H. Stolley, H. Cailloud.—p. 143.
Changes of Blood Coagulation Factors in Poliomyelitis. Fr. Koch, H. E. Schultze, G. Schwick.—p. 145.
Disturbances of Mineral Metabolism Due to Central Factors. H. Hungerland, H. Vogtherr, and H. Weber.—p. 147.
Cerebrospinal-Fluid Sugar: Free and Protein-Bound Fraction in Central Nervous System Diseases. H. Kellner.—p. 149.
Treatment of Tuberculous Meningitis with ACTH. W. Heck.—p. 149.
Special Features of Icterus Neonatorum in Children with Congenital Hypothyroidism. W. Swoboda and H. G. Wolf.—p. 152.
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Precocious Puberty and Adrenogenital Syndrome:
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2. Early-Normal Sexual Development and Precocious Puberty. H. P. G. Seckel.—p. 165.
3. Adreno-Genital Syndrome. Clinical Picture and Pathogenesis. J. R. Bierich.—p. 170.
Physiology and Pathophysiology of the Adrenal Cortex in Children. H. Zeisel.—p. 179.
Normal Endocrinological Findings in Pre-Puberty and Puberty. A. Schwenk and Ohndorf.—p. 182.
The History of Five Patients with Precocious Puberty. H. Orel.—p. 182.

104:187-222 (April) 1956

Clinical Studies of the Value of the "Second Carbohydrate." Th. Brehme and A. Pauli.—p. 187.
Uretero-Pelvic-Renal Statis in Urinary Tract Tuberculosis in Children. R. Ottenjahn and G. Hasche-Kluender.—p. 189.
Cold Agglutinins in Wissler's "Subsepsis Hyperergica." Friedrich-Wilhelm Wedemeyer.—p. 193.
The Welfare of Children with the Asthmatic Symptom Complex. F. Kreuser.—p. 195.
Metabolic Studies on the Use of Nonspecific Animal Serum in Infants. G. Erdmann and W. Heine.—p. 201.
Comparative Observations on the Use of Human Breast Milk and a Cow Milk Preparation Similar to Human Breast Milk in Premature Infants. Peter Paul.—p. 206.
* What is the Significance of Staphylococcus Aureus in the Stool of Infants? K. Hoffmann and H. U. Sauerbrei.—p. 211.
Staphylococcus Aureus in the Stool of Infants and Young Children: Significance and Misinterpretation. Malte Kienitz.—p. 214.
Review Article: The Gastrointestinal Tract. E. Hoen.—p. 219.

Experiences with the German Polio Vaccine.—Polio vaccine produced in Germany by the Behring Company as outlined by Haas differed from the American Salk vaccine in that the German product had aluminum hydroxide ($Al[OH]_3$) powder added as an adsorbent.

The purpose of this adjuvant was twofold; 1. to produce slower absorption of the vaccine and to facilitate more effective antibody formation; 2. to increase safety of the vaccine.

More than 100,000 people, the majority children, received the vaccine. No untoward reactions and no cases of paralytic polio were reported in this group. The second injection was given two weeks after the first and the third five weeks later.

Antibody titers were determined in 574 patients of the vaccinated group and in 347 patients with poliomyelitis. No antibodies had been found in these patients prior to vaccination respective to illness. It was found that 60.8% of vaccinated patients produced neutralizing antibodies as compared with 75.5% of patients who had been afflicted with the disease as proved by clinical findings and virus isolation.

Breakdown of these figures according to the three types of polio virus revealed that for Type I 75% had neutralizing antibodies after the disease and 39% after vaccination; of Type II 89% after the disease and 91% after vaccination; of Type III 72% after the disease and 40% after vaccination.

Complement-fixing antibodies were found to rise more slowly and to a lesser height after vaccination than after the natural disease. 86.6% of polio patients and 80% of vaccinated patients were found to have complement-fixing antibodies.

What is the Significance of Staphylococcus Aureus in the Stool of Infants?—Of 4748 infant stools 228 specimens from 100 patients (4.8%) were found to have more than 100 colonies of Staphylococcus aureus per plate. The culture medium was one rich in salt. All of these infants had been hospitalized because of various illnesses. One-half of this group with the organisms in their stools had not received antibiotics.

Of 99 stools from clinically healthy newborn infants 7 (7%) were found to have Staphylococcus aureus. Of 73 stools from infants attending Well Child Clinics and Breast Milk Collection Stations Staphylococcus aureus was found in 2 (2.7%). Of 142 premature infants without gastrointestinal tract disturbances 40 had Staphylococcus aureus in their stools; 31 had never received antibiotic therapy. Of 3100 stools of adults with various gastrointestinal disturbances Staphylococcus aureus was found in 24 (0.77%).

It was felt that the appearance of heavy growths of Staphylococcus aureus in the stool of infants usually began after hospitalization and was transmitted via gastrointestinal (feedings) and air-borne routes. In view of the frequency of the occurrence of Staphylococcus aureus in the stools of infants, pure Staphylococcus aureus should be considered a rare disease most likely due to heavy contamination of food.

New England Journal of Medicine, Boston

255, No. 1 (July 5) 1956

Rural Health Work in India. Maria Selvaneyagam.—p. 25.
The Growing Importance of Cardiovascular Radiology. Fred J. Hodges.—p. 28.

255, No. 2 (July 12) 1956

Medical Progress: Allergy. Walter S. Burrage, J. E. Greene, Leo B. Burgin, Irving H. Itkin, Harold S. Novey, Joseph Engler, and John W. Irwin.—p. 79.
Porphyrin Excretion and Hemoglobin Synthesis in a Case of Acute Intermittent Porphyria. Frank L. Iber, Emile Taxay, Kurt Nassau, and Irvin C. Plough.—p. 86.
* **Current Concepts in Therapy: Penicillin.**—p. 88.

255, No. 3 (July 19) 1956

Problems in Anesthesia for Operations on the Heart. Leroy D. Vandoon and Thomas K. Burnop.—p. 110.
* **Prophylaxis of Isoniazid Neuropathy with Pyridoxine.** H. Blair Carlson, Eleanor M. Anthony, William F. Russell, and Gardner Middlebrook.—p. 118.
Medical Progress: Allergy. Walter S. Burrage, J. E. Greene, Leo B. Burgin, Irving H. Itkin, Harold S. Novey, Joseph Engler, and John W. Irwin.—p. 128.

255, No. 4 (July 26) 1956

Medical Progress: Diabetes Mellitus. Samuel B. Beaser.—p. 173.

255, No. 5 (Aug. 2) 1956

* **The Nephropathy of Potassium Depletion: A Clinical and Pathological Entity.** A. S. Relman and W. B. Schwartz.—p. 195.
The Antiarrhythmic Action of Amboneatyl (2-Diethylaminoethylisonicotinamide, MC-4112). A. Sjoerdsma, H. Maling, H. W. Pratt, J. Axelrod, H. J. Kayden, and L. L. Terry.—p. 213.

Chemical Control of Pulmonary Ventilation: I. The Physiology of the Chemoreceptors. H. Winterstein.—p. 216.
Diabetes Mellitus. S. B. Beaser.—p. 223.

255, No. 6 (Aug. 9) 1956

Syndromes Associated with "Allergic" Vasculitis. R. P. McCombs, J. F. Patterson and H. E. MacMahon.—p. 251.
* Eastern Equine Encephalomyelitis in Massachusetts in 1955: Report of Two Cases in Infants. W. D. Winter Jr.—p. 262.
Chemical Control of Pulmonary Ventilation: II. Hypoxia and Respiratory Acclimatization. H. Winterstein.—p. 272.
Anesthesiology. A. B. Stevens and U. H. Eversole.—p. 278.
Thyroid Function in Legg-Perthes Disease. E. M. Chapman.—p. 289.
Current Concepts in Therapy.—p. 290.

255, No. 7 (Aug. 6) 1956

* Some Observations of the Behavior of Amylase in Relation to Acute Renal Insufficiency. W. H. Meroney, N. L. Lawson, M. E. Rubini, and J. V. Carbone.—p. 315.
Present-Day Management of Pleural Empyema in Infants and Adults. G. E. Lindskog.—p. 320.
Novobiocin in the Treatment of Surgical Infections Due to Staphylococci and Other Gram-Positive Bacteria. A. M. Rutenburg, P. Shapiro, and F. Schweinburg.—p. 325.
Chemical Control of Pulmonary Ventilation: III. The "Reaction Theory" of Respiratory Control. H. Winterstein.—p. 331.
Management of Pyelonephritis. H. A. Derow.—p. 337.
Urologic Examination with the New Radiopaque Mediums, Diatrizoate, Acetrizoate and Diprotrizoate: A Clinical Comparison. H. A. Hoffman, S. J. Koczera, N. L. Portnoy, W. Simas, and A. R. Hastreiter.—p. 343.

New England Journal of Medicine, Boston

255, No. 10, (Sept. 6) 1956

Eyeball Bruits. J. H. Cohen and Stanley Miller.—p. 459.
* Endocardial Fibroelastosis in Infants Associated with Thrombosis and Calcification of Arteries and Myocardial Infarcts. W. A. Thomas, K. T. Lee, M. H. McGavran, and E. R. Robin.—p. 464.
Medical Progress: Neurology. W. K. Jordan and H. H. Merritt.—p. 468.
Observations on the Reliability and Safety of Bladder Catheterization of The Urine. L. B. Guze and P. B. Beeson.—p. 474.

Current Concepts in Therapy: Penicillin.—The authors discuss penicillin. It is a valuable and most widely used drug. Two forms are used: (1) benzyl penicillin or penicillin G; and (2) phenoxymethyl penicillin or penicillin V. Penicillin deteriorates rapidly in water. In the body over 50% is found in combination with serum albumin. It is widely disseminated in the body, although only a fraction gets into the normal spinal fluid. It is excreted by the kidney tubules. Drugs such as probenecid, by blocking tubular excretion, are effective in retaining the drug in the blood stream for longer periods.

Penicillin is primarily effective against Gram-Positive organisms. It is also highly effective against Gonococcus and Meningococcus; also effective against Actinomyces, Borrelai, Spirillum, and Treponema. Little resistance to it has been developed by the Streptococcus, Meningococcus, Gonococcus and Pneumococcus. The Staphylococcus, however, has in a high percentage of cases, especially in hospitals, proved resistant. It has no effect against the common viral diseases.

Relatively speaking, penicillin is a safe drug but more than 200 cases of anaphylaxis and 50 deaths have been reported from its use (all but 2 from parenteral administration). Urticaria develops in about 6%, serum-sickness-like reactions in 0.1%, and hepatitis, agranulocytosis, necrotizing angiitis, and other rare complications in occasional patients. Applied to the skin, sensitivity occurs in 10% or more.

As far as dosage is concerned most infections are controlled by 800,000 units a day in two doses. Benzathine penicillin G (Bicillin) gives prolonged levels but they are apt to be very low.

The authors felt that the oral route was often adequate. Buffered penicillin G must be given on an empty stomach, but penicillin V can be administered irrespective of meals. The authors feel that penicillin should not be mixed together with any drugs in fixed ratios.

Prophylaxis of Isoniazid Neuropathy with Pyridoxine.—The authors report that with dosages of isoniazid of 8 mg. per kilogram of body weight or over peripheral neuropathy often occurred. Peripheral neuropathy was usually manifested by numbness and tingling, especially in the extremities. They state that 25 mg. of pyridoxine a day cut down markedly the incidence of peripheral polyneuritis when the patient was getting 8 mg. isoniazid per kilogram per day and that 50 mg. of pyridoxine a day usually prevented peripheral polyneuritis when

the isoniazid dosage was 16 mg. per kilogram per day. In some of the cases, either giving or increasing pyridoxine has been successful in clearing up signs of neuropathy.

The Nephropathy of Potassium Depletion: A Clinical and Pathological Entity.—This is a report of the clinical and functional aspects of the renal disease associated with potassium depletion in man. These findings were correlated with the histologic changes found in renal tissue obtained by serial biopsies. The authors report five cases followed with serial renal functions; three of the cases had renal biopsies. All cases had prolonged diarrhea, two associated with sprue and three with excessive laxatives. Other symptoms were weakness, malaise, vague muscle pains. Five of thirteen patients (combined from literature) had polyuria; five had slight to moderate peripheral edema. The most specific urinary finding was a fixed specific gravity (1.014 upper limit); there was minimal albuminuria frequently. Urea, creatinine, and inulin clearances are reduced. There may be some sodium retention. On renal biopsy three of the cases showed tubular lesions, one being a vacuolar lesion in the tubular cytoplasm, and the other two a nonspecific, degenerative cytoplasmic lesion. These lesions cleared up after repair of the potassium deficit, as did the evidences of impaired renal function. The authors discuss the production of tubular lesions in animals by potassium deficiency. They also mention the fact that magnesium is said to produce renal lesions and note that one of their cases had a low magnesium. However, they felt that they had eliminated all other causes for the renal abnormalities and cite the literature as further support.

They give a list of clinical states that may be associated with renal lesions probably due to low potassium. They are as follows:

1. Diarrheal diseases—ulcerative colitis, regional enteritis, cholera, bacillary dysentery, sprue syndrome, Whipple's disease, malabsorption syndrome.

2. Hyperadrenalism—cortisone treatment, primary aldosteronism.

3. Renal disease with potassium wasting—Fanconi syndrome, renal tubular acidosis, cystinosis.

4. Renal disease with extrarenal potassium wasting (vomiting and diarrhea)—subacute and chronic glomerulonephritis, lower nephron nephrosis, chronic pyelonephritis, and hydronephrosis.

5. Versene poisoning (sodium salt).

Eastern Equine Encephalomyelitis in Massachusetts in 1955: Report of Two Cases in Infants.—The author reports two cases of eastern equine encephalomyelitis in Massachusetts during the poliomyelitis epidemic of 1955. The first case died. Diagnosis was made by the injection of brain suspension into mice. The second case has remained comatose. Diagnosis was made by the development of a titer to the virus in the convalescent-phase serum. These results are comparable to the usual course of the disease—acute febrile illness, with rapid development of coma and convulsions that is frequently fatal, occasionally allows survival with permanent brain damage, and less frequently subsides with complete recovery. The clinical symptoms are indistinguishable from other causes of encephalitis. A helpful finding in the acute stage is a marked rise in the peripheral and spinal fluid white blood cell counts. In the first case admission white blood cell count was 18,000 with a spinal fluid count of 30 (40% neutrophils); in six hours the spinal fluid count was 1550 cells with 94% neutrophils. In 17 hours the peripheral white count was 45,000 with a marked shift to the left and the spinal fluid count was 2100 with 60% neutrophils. The second case was seen later and did not show these changes.

In discussing the epidemiology several factors were brought out. Since 1938 there has continued to be a scattering of cases in horses and mules in Massachusetts. It has also been found in domesticated pheasants and in a catbird. It was noted that 1938 and 1955 were exceptionally wet summers.

The author points out that the mosquito is known to carry the virus but that species differ in their susceptibility to acquire the virus and also in the dose of virus they can inoculate. Man and horses are apparently "indicator" species, for the titer of viremia is not high enough to infect mosquitoes. In birds, the large wading birds in endemic areas have a high percentage of neutralization titers, whereas the small songbirds are very susceptible. The grackle, however, is in between, often maintaining a titer far higher than the mosquito infective level but failing to succumb.

It has also been shown that other ectoparasites may harbor the virus, particularly chicken mites and lice, and this may explain the "wintering over" problem. However, one group of workers have found bird mites to be very inefficient vectors.

Experimental data also seems to indicate that the variations in severity of the disease may, in part, be a function of the dose of the inoculum.

Although not entirely clear, it seems that conditions necessary for the appearance of the disease is an abundance of mosquitoes, favored by an abnormally wet period, followed by a warm dry spell.

Active immunization is feasible, if necessary. Diagnosis is essentially a laboratory one.

Some Observations of the Behavior of Amylase in Relation to Acute Renal Insufficiency.—The authors report on the finding of high plasma amylase levels in patients with acute renal failure, a finding which is known to occur in chronic uremia, but has not been investigated in the acute disease. In one case signs of peritonitis were present and, together with high plasma levels of amylase, suggested pancreatitis. The symptoms, however, subsided after artificial-kidney dialysis. The high levels of amylase fluctuated from time to time without any apparent relation to the height of the azotemia.

In experiments on dogs the authors found high plasma amylase levels. Here again, the levels did not parallel the level of azotemia.

The reported cases that died had no evidence of pancreatitis at autopsy. No other cause for increase (such as opiates) was found in most cases.

In experiments with dialysis it was found that amylase did not cross membranes which are permeable to all the substances filtered by the glomeruli, a fact which suggested that the excretion of this material into the urine might be due to tubular function.

Also it was found that amylase did not cross the dialyzing membrane of the artificial kidney, yet in some cases that were dialyzed serum concentrations dropped markedly but in others it did not.

The authors point out that a high level of amylase in cases of acute renal failure, associated with abdominal pain, is not diagnostic of pancreatitis.

Endocardial Fibroelastosis in Infants Associated with Thrombosis and Calcification of Arteries and Myocardial Infarcts.—In a survey of autopsied patients who died with myocardial infarcts, the authors discovered two infants who had died with acute myocardial infarcts resulting from advanced disease of the coronary arteries with calcification. Both infants were boys; one died at *2* months, the other at *3* months, both having been considered as well before the terminal illness. One infant was sick for *2* weeks, the other for 12 hours. The heart of each infant was greatly hypertrophied. Grossly multiple partial occlusions were noted in the coronary arteries of each infant. Microscopically, in both infants, focal changes were noted in the coronary arteries; organized thrombi containing calcium were recognized; marked intimal thickening was noted in other foci, and in many vessels the elastic and muscular coats were partially or completely destroyed and replaced by fibrous tissue containing calcium. In both infants foci of necrosis were noted in the myocardium. The left ventricular endocardium of each infant was markedly thickened by fibrous and elastic tissue. Arteries in other sites in both infants, pancreas, adrenal glands, skeletal muscle, and pelvic connective tissue showed the same type of changes.

The authors compared these cases with two infants whose left coronary artery arose from the pulmonary artery, with 24 infants with endocardial fibroelastosis without other defects, and with one infant with endocardial fibroelastosis complicated by myocardial infarction without calcific arterial lesions. Only in the latter case were the coronary arteries involved and in this case the lesions were consistent with organized thromboemboli. The authors injected fragments of rabbit blood clots into the left ventricle of other rabbits and produced infarcts of the myocardium with calcium but did not produce thickening of the endocardium.

The authors suggested several possibilities: (1) myocardial infarcts resulted in the development of endocardial fibroelastosis (discarded this because lesions in endocardium appeared older); (*2*) the calcific arterial disease alone caused the endocardial fibroelastosis (discarded for same reason as in 1); (*3*) endocardial fibroelastosis resulted in the development of calcific arterial disease with myocardial infarction—postulated that this could result from emboli from mural thrombi attached to the diseased endocardium (no thrombi were seen in the two cases, however), and (4) some unknown agent caused both.

Pediatrics, Springfield, Ill.

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* Delayed Effects Occurring Within the First Decade After Exposure of Young Individuals to the Hiroshima Atomic Bomb. R. W. Miller.—p. 1.
Development of Antibodies to Enteric Pathogens. R. Yeivin et al.—p. 19.
Multiple Sclerosis. N. L. Low et al.—p. 24.
Dosage of Neostigmine. P. R. Patterson et al.—p. 31.
Plasma Values in Prematures. J. B. Pincus et al.—p. 39.
Sulfonamide Administration in Newborns and Prematures. E. G. Fichter et al.—p. 50.
Localized Paralysis in Poliomyelitis after Inoculation. F. A. Neva.—p. 59.
Effect of Extracts of Hemophilus Pertussis on Leukocyte Counts. W. L. Bradford et al.—p. 64.
Isoniazid Poisoning. B. E. Katz et al.—p. 72.
Isoniazid Poisoning. S. Livingston et al.—p. 77.
Methyl Salicylate Poisoning. A. K. Done et al.—p. 80.
Care for Adolescents. A. Roth et al.—p. 86.
Investigation in Practice. J. C. Wilcox.—p. 90.
Education—Institutes on Care of Prematures. A. Yankauer et al.—p. 95.
Public Health—Convalescent Care. H. M. Wallace et al.—p. 102.
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Report—Committee on Nutrition.—p. 159.

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Carbohydrate Metabolism in the Newborn. M. Cornblath. et al.—p. 167.
Hyperimmune Vaccinal Gamma Globulin. C. H. Kempe et al.—p. 177.
Sweat Test in Fibrocystic Disease of the Pancreas. G. J. Barbero et al.—p. 189.
Indirect Arterial Pulse Tracings in Diagnosis of Congenital Heart Disease, I. L. A. Kuhn et al.—p. 193.
Indirect Arterial Pulse Tracings in the Diagnosis of Congenital Heart Disease, II. E. Donoso et al.—p. 205.
Hereditary Nystagmus. J. N. Lein et al.—p. 214.
* Further Observations on Electrolyte Change in Tuberculous Meningitis. D. B. Cheek.—p. 218.
Roentgenographic Manifestations of Congenital Megacolon. C. Z. Berman.—p. 227.
Sickle Cell Anemia, VII. M. E. Jenkins et al.—p. 239.
Erysipelatous Skin Necrosis. I. F. Burton et al.—p. 249.
Brain Tissue in the Nose and Throat. N. L. Low et al.—p. 254.
Atresia of the Vagina in Infancy. R. H. Whittlesey et al.—p. 260.
Review—Iron Metabolism and Requirements. P. S. Sturgeon.—p. 267.
Commentary—Iron Metabolism. I. Schulman.—p. 299.
Education—Teaching of Pediatric Pathology. T. C. Wyatt et al.—p. 301.
Treatment of Megaloureters. O. Swenson et al.—p. 304.
Role of Genetics in Disease. J. Warkany et al.—p. 314.
Pediatric Gynecology. R. B. Greenblatt et al.—p. 318.
Mental Health. R. E. Wolf et al.—p. 323.

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Editorial. C. D. May.—p. 345.
Vascular Hemophilia. I. Schulman et al.—p. 347.
* Weight Gains in the First Four Weeks of Infancy: A Comparison of Three Diets. R. T. Gross et al.—p. 362.
Familial Nonhemolytic Jaundice. B. Childs et al.—p. 369.
Congenital Nonhemolytic Jaundice. I. M. Rosenthal et al.—p. 378.
Distinctive Type of Biliary Cirrhosis in Cystic Fibrosis of the Pancreas. P. A. di Sant' Agnese et al.—p. 387.
Patent Ductus Arteriosus. R. C. Anderson et al.—p. 410.
Chronic Nonspecific Diarrhea. S. Q. Cohlan.—p. 424.
Determination of Biliruhin in Serum. D. Hsia et al.—p. 433.
Epidemic of Streptococcal Infections. W. H. Langewisch.—p. 438.
Hypoparathyroidism and Glaucoma. J. L. Rhyne et al.—p. 448.
Nephrotoxic Sera in Experimental Nephrosis. M. B. Rothenberg et al.—p. 455.
Carcinoma of the Thyroid. T. Winship.—p. 459.
Observing, Interviewing and Advising Parents—An Attitude Study. B. M. Korsch.—p. 467.
Review—Congestive Heart Failure. J. D. Keith.—p. 491.
Commentary—The Problem of Nodules in the Thyroid. E. B. Astwood.—p. 501.
Public Health—Retrolental Fibroplasia. M. E. Wegman.—p. 506.
American Academy of Pediatrics Report—Committee on Nutrition.—p. 509.

Delayed Effects Occurring Within the First Decade After Exposure of Young Individuals to the Hiroshima Atomic Bomb.—This report summarizes the previously reported effects of exposure to the atomic bomb as studied by the Atomic Bomb Casualty Commission and is an extension of this work in which various effects of exposure are reported in persons who were 10 years of age or less, including those who were in utero at the time

of the Hiroshima bombing. Included are studies of the incidence of microcephaly in infants in utero, blood diseases, abnormalities of the eye, susceptibility to infection, tumors, and sequelae of blast and heat of the bomb. These effects are reported in relation to the distance from the hypocenter at the time of exposure.

These data reveal that there is a definite increase in microcephaly and associated mental retardation in persons exposed in utero and that this is the only significant defect noted as yet in this group. Also, it is indicated that there is a definite increase in leukemia in young persons exposed, excluding those in utero. Both of these effects were definitely related to the distance of the person from the hypocenter, the incidence varying inversely with the distance.

No cataracts were noted in this group and no increased incidence of infection was found. There was no increase in tumor incidence. Various traumatic sequelae from blast and heat effects were noted.

Further Observations on Electrolyte Change in Tuberculous Meningitis.—This paper represents an extension of the author's previous work in which it has been shown that tuberculous meningitis is often accompanied by low concentrations of sodium and chloride in the serum and spinal fluid with a metabolic alkalosis but without a reduction in total content of chloride of the body. From this previous work it is concluded that in tuberculous meningitis a hypotonic expansion of the extracellular fluid takes place, but it is not known whether or not this is at the expense of intracellular water. The present article presents further data concerning concentrations of electrolytes in serum, volume of the bromide space, and the total content of water and chloride in the body gathered from the study of eight additional patients with tuberculous meningitis. Studies of the serum bromide/spinal fluid bromide ratio are also included.

The above disarrangements of electrolytes were confirmed in this series of patients. Studies of the serum bromide/spinal fluid bromide ratio revealed that this ratio, found to be 4:1 in normal circumstances, approached unity in tuberculous pneumonitis, but was significantly lowered in two of five patients with purulent meningitis.

In the discussion it is pointed out that the finding of hyponatremia, hypochloremia with metabolic alkalosis, in association with hypotonic expansion of the chloride space, may be of assistance in establishing the diagnosis of tuberculous meningitis, but it is felt that the permeability of the blood spinal fluid barrier is not, per se, reliable as a diagnostic criterion. A discussion of the possible mechanisms of electrolyte derangements is presented, and while no conclusions can be reached it is felt that failure to conserve potassium may be important. It is pointed out that needs for potassium should be more than adequately fulfilled and that loads of sodium above that required for maintenance should be avoided in these patients.

Weight Gains in the First Four Weeks of Infancy: A Comparison of Three Diets.—Newborn infants were assigned one of the following diets: breast milk, evaporated milk and water with 5% added carbohydrate, and a modified evaporated milk (Bremil). No other foods were given and the same amounts of vitamins were given to all infants. At approximately 4 weeks the infants were seen again and weights recorded; a careful statistical analysis of weight gain in the three groups, which were subdivided further according to race, sex, and parity, was done. A total of 407 infants were included in the study.

Results of this study revealed no significant difference in weight gain in either of the three groups after 4 weeks. It was emphasized that this study was restricted entirely to weight gain with no attempt to assess the superiority of any particular diet with regard to other factors.

Radiology, Syracuse, N. Y.

67, No. 1 (July) 1956

* Idiopathic Coxa Vara in Childhood. N. Finby, H. G. Jacobson, and M. H. Poppel.—p. 10.
Bilateral Embryoma of the Kidney: Patient Alive and Well Three Years After Treatment. M. B. Close, C. A. Peterson, and R. P. Johnson.—p. 99.

67, No. 2 (Aug.) 1956

* Infantile Arteriosclerosis. H. S. Weens and C. A. Marin.—p. 168.
* Progressive Diaphyseal Dysplasia (Engelmann's Disease). E. B. Singleton, J. R. Thomas, W. W. Worthington, and J. R. Hild.—p. 233.

Idiopathic Coxa Vara in Childhood.—Idiopathic coxa vara, by definition, indicates a diminution in the angle of inclination of the femoral neck and shaft below the normal 120 degrees, with the epiphyseal cartilage plate assuming an increasingly vertical position and relative elevation of the greater trochanter. In almost all patients there is irregularity and fragmentation of the metaphyseal-epiphyseal junction and often widening of the epiphyseal cartilage plate. Deformity increases with weight bearing. The femoral neck is usually short and deformed, occasionally almost completely absent. The femoral head is of normal density but generally hypoplastic and slightly deformed. Sclerotic stress changes usually show up along the inferior margin of the femoral neck. Stress fractures may develop.

Of the author's 23 cases 7 were considered to be congenital in origin, 16 developmental, the difference depending upon the presence or absence of other associated anomalies. The congenital type is characteristically seen at birth or shortly after, while in the developmental type the process is usually not apparent until the age of 3 or 4 years. Both types are distinct, though they may represent different stages of the same process and thus have certain features in common.

The most pertinent physical findings are shortening of the lower extremity and limitation of abduction and/or internal rotation of the hip and limping. Irregularity and fragmentation of the proximal metaphysis often bring about a loose triangular fragment of bone at the margin of the metaphysis. A tenable hypothesis of deficient osteogenesis is suggested, but the pathology and pathogenesis are not clearly understood.

The optimum treatment at present is subtrochanteric osteotomy, at an early age.

Infantile Arteriosclerosis.—Calcification and sclerosis of the arteries in infants and young children which may be encountered in a variety of clinical conditions is often associated with disturbances in calcium and phosphorous metabolism. Thus arteriosclerosis has been recognized in renal disease, hyperparathyroidism, and vitamin D intoxication. Similar changes in the arteries have been observed in progeria associated with extensive growth disturbances. Aside from these, infantile arteriosclerosis has been found in an increasing number of cases in which no obvious etiological factors are apparent.

The principal morphologic changes of the arteries are marked disorganization of the internal elastic membrane, deposition of lime salts, and fibroblastic proliferation of the intima. The vascular lumen becomes markedly narrowed or obliterated.

While a large majority of these cases have not been diagnosed before necropsy, the arteries are clearly visible on roentgenograms and this is the most important means of establishing a diagnosis during life.

One of the author's two cases, a 10-month-old Negro boy, died after a prolonged period of failing health, cardiac hypertrophy, and hypertension. The other, a 25-day-old white boy, died after an intracranial hemorrhage. The clinical history in several instances in previous reports of 40 cases has shown that siblings have died under similar circumstances. This observation suggests that genetic factors may predispose to the development of the condition. In a large number of patients, particularly those with severe coronary artery disease, the onset of the symptoms was sudden, with the development of cyanosis, dyspnea, and lethargy, suggesting acute cardiac failure. In others in whom there was a more subacute or chronic course, the clinical picture was largely of impaired health, with anorexia, vomiting, weight loss, and general debility. Cardiac enlargement and edema has been repeatedly observed and in several instances electrocardiographic studies disclosed myocardial damage.

Progressive Diaphyseal Dysplasia (Engelmann's Disease).—In view of the many perplexing aspects of this bizarre disease and the lack of knowledge regarding its etiology, an additional case is reported, making 14 cases reported to date.

A boy, 5½ years of age, entered the hospital because of a peculiar gait. This came on gradually and had attracted attention when he was 2 years old. Tiredness, ankle pain, and leg cramps were the subjective symptoms. The opinion of several physicians was that he had postparalytic poliomyelitis. A review of systems was normal excepting for shortness of breath, with vague chest pain and tachycardia. The patient was thin and undernourished. He walked as though "stiff at the knees and flat footed."

Radiographic studies showed symmetrical fusiform sclerosis involving the diaphysis of each tibia, fibula, femur, humerus, ulna, and radius. The cortex was thickened and the medullary cavity narrowed. Multiple areas of rarefaction were scattered throughout the sclerotic areas.

There was fusiform enlargement of the diaphysis. The involvement was greater in the femora and tibiae. The hands, feet, pelvis, scapulae, clavicle, ribs, and vertebrae were normal.

A biopsy of bone and soft tissue led to the conclusion that the disease was not limited to the osseous system. The confinement of the sclerotic process to the diaphysis can perhaps be explained on a vascular hypothesis. Vascular sclerosis as a cause cannot be ruled out, since the vessel walls were markedly thickened.

Whatever the cause may be the author concludes that this disease is not limited to the osseous system, since the skeletal muscles are undeveloped and could easily account for the fatigue and waddling gait. The etiology is entirely obscure.

Rivista di clinica pediatrica, Firenze, Italy

57, No. 1 (Jan.) 1956

* Cortisone and ACTH in the Treatment of Tuberculosis in Children: Views as to Cortisone Therapy Under Antibiotic Protection. C. Cocchi.—p. 1.
The Alkali Reserve: Diffusible Calcium Ratio and Its Relation to Ionic Calcemia. G. Mangione, S. Le Brun, N. Loddi, and A. Pandolphini.—p. 21.
Clinical, Hematological and Serological Observations During an Epidemic of Rubeola. G. Biscioni and E. Tosi.—p. 28.
Secondary and Subclinical Forms of Acquired Immunologic Hemolytic Anemias. G. Gelli.—p. 40.
Two Cases of Osteogenesis Imperfecta. G. Aceto and A. Zicaulella.—p. 53.
The Serum Proteins and Lipoproteins During Underfeeding in an Infant During the First Week of Life. P. Moggi.—p. 64.

57, No. 2 (Feb.) 1956

* On the Diagnosis of Toxoplasmosis. A. Gentili.—p. 177.
* Congenital and Acquired Toxoplasmosis. A. Gentili.—p. 197.
* A Case of Toxoplasmosis in an Infant. G. Baldasseroni and L. Francalancia.—p. 212.
* Antiviral Chemotherapy. P. Cocchi.—p. 238.
Experimental Studies on the Action of Prednisone. G. Bartolozzi and L. Francalancia.—p. 250.
Penicillin Blood Levels in Children After the Oral Administration of Penicillin. V. C. Calzolari, C. Guazzelli, and M. Acocella.—p. 283.

57, No. 4 (April) 1956

Anoxia in the Newborn. P. Moggi.—p. 683.
*The Effects of Cortisone and of Prednisone on Tuberculin Reactions in Guinea Pigs Infected by Koch's Bacilli. G. Bartolozzi.—p. 705.
A Case of Hemolytic Anemia, with Jaundice, Which Was Resistant to Splenectomy. M. Dettori.—p. 716.
The Treatment of Dystrophic Infants by Blood Transfusions. R. Bartalena and C. Cipolloni.—p. 729.
Ewing's Tumor Originating on a Rib. G. Lischi and G. Menichini.—p. 741.
A Device for the Collecting of the Feces of Infants. B. Bucci.—p. 754.

Cortisone and ACTH in the Treatment of Tuberculosis in Children: Views as to Cortisone Therapy Under Antibiotic Protection.—With the use of cortisone, and especially of hydrocortisone, the percentage of cures in cases of tuberculous meningitis in the pediatric clinic in Florence now exceeds 97%.

The correct dosage of the hormone is very important. Too big a dose is dangerous, because of the drug's "pro-infective" action. The hormone must always be accompanied by protective antibiotic therapy.

The therapeutic course at present recommended is as follows: (a) streptomycin 300-500 mg. and isoniazid 500-900 mg. daily I. M. or by I. V. drip. (b) streptomycin sulphate 20-30 mg. and isoniazid 20-40 mg. by lumbar puncture. (c) isoniazid 20 mg. and hydrocortisone 2.5 mg. by cisternal puncture.

The lumbar and cisternal injections are alternated every 12 hours. The cisternal injections of the hydrocortisone have definitely kept down the tendency to blockage in the meninges.

On the Diagnosis of Toxoplasmosis.—Congenital and Acquired Toxoplasmosis.—In these two articles, Gentili reports four carefully studied cases of toxoplasmosis. Since the signs of this disease are so varied, he speaks of a clinical diagnosis as being "diabolically" difficult. The finding of the protozoal parasite in a living patient is rare; but the color reaction test of Sabin and Feldman has proved most dependable. One of his patients, a 5-year-old, had hepatomegaly and blood cell changes, death being due to hemorrhages. A second patient, a 9-year-old, was mentally retarded and had pigmented retina; it was a congenital case, both parents as well as the child giving positive Sabin tests. The third child, 9 years old, clinically showed only chorioretinitis; this was also a congenital case, as shown by the Sabin test. The

fourth child was 8 months old, an infant with hydrocephaly, intracranial calcification, and chorioretinitis.

A Case of Toxoplasmosis in an Infant.—The case of a 2-months-old infant with toxoplasmosis is reported from Milan; an autopsy report is included. Electrophoretic studies of the blood serum revealed a low albumin and a high alpha- and gamma-globulin contents.

Antiviral Chemotherapy.—Tests were made as to the possible chemotherapeutic value of four antimitotic substances—6-mercaptopurine, Aminopterin, triethylene melamine and thiosemicarbozone. The thought was that, since these chemicals inhibited the synthesis of nucleinic acids, they might also react against virus reproduction. The observations were made on rabbits, which had been inoculated with smallpox vaccine. The 6-mercaptopurine did delay to some extent the appearance of the vaccination pustule.

The Effects of Cortisone and of Prednisone on Tuberculin Reactions in Guinea Pigs Infected by Koch's Bacilli.—It was observed that the tuberculin tests were markedly less positive after cortisone had been given to guinea pigs which had previously been inoculated with tubercle bacilli. Prednisone had an even more inhibiting effect on the tuberculin reaction. The change was equally as pronounced when the animals had been receiving streptomycin therapy.

News and Comment

ANNOUNCEMENTS

Course in Neuromuscular Diseases.—The Cook County Graduate School of Medicine announces an intensive course in neuromuscular diseases of children with special emphasis on cerebral palsy, to be given by Dr. Meyer A. Perlstein for the two-week period from July 8 to 19. This is an intensive didactic and clinical course designed for pediatricians, orthopedists, neurologists, psychiatrists, and physiatrists interested in the care and treatment of children with neuromuscular handicaps. Emphasis will be placed on the practical clinical aspects of treatment and rehabilitation procedures. The course will include itinerant clinics to round out the program in most of its practical aspects. The fee for the course, which is $250, will include the cost of luncheons during the two-week period, as well as the expense of travel, meals, and accommodations during the trip to the field clinic. For further information, write to John W. Neal, Registrar, Cook County Graduate School of Medicine, 707 S. Wood St., Chicago, Ill.

Pediatric Research Award.—In science there is a special reward for participation, the satisfaction of working in an area dedicated to the increase of knowledge and its application to the betterment of human life. Too often, however, good work goes unrecognized, or the pressures of continuing endeavor prevent its dissemination. To encourage scientific work by young investigators and to show a small measure of appreciation for fruitful scientific effort, the Ross Award in Pediatric Research is established.

Each year the Western Society for Pediatric Research will confer this award on a chosen nominee in recognition of outstanding research accomplishment in a field related to pediatrics. The nominee shall not be over 35 years of age and during the progress of his research shall have resided for at least one year in the geographic area represented by the Society. The work need not have been published. The Ross Laboratories will donate $1000 and a suitably engraved plaque to be presented to the nominee at the annual meeting of the Society.

The Award winner will be asked to submit a paper concerning some phase of his work or a summary of it to the Western Society for Pediatric Research. If circumstances permit, the recipient and the Western Society for Pediatric Research will submit this paper for inclusion on the program of the next annual meeting of the national Society for Pediatric Research.

Nominations may be tendered by any interested member of the Western Society for Pediatric Research. Nominations should be submitted in quadruplicate and include all supporting data and a clear statement of the reasons why the candidate is considered worthy of the award, designating the particular aspects of his work which are considered outstanding.

Nominations will have closed April 30 in order to give the Committee sufficient time to come to a decision prior to the annual meeting in the fall. The award may be given jointly to two or more investigators at the discretion of the Committee or it may be omitted if the Committee considers that a worthy candidate has not been presented. Please mail directly to Robert H. Alway, M.D., Secretary-Treasurer, Western Society for Pediatric Research, 2351 Clay St., San Francisco, Calif.

Short Refresher Courses.—The following short refresher courses will be given at The Children's Hospital of Philadelphia in May and June, 1957.

1. Pediatric Advances for Pediatricians and General Practitioners. May 27 through May 31, 1957. Conducted by the Staff of the Children's Hospital of Philadelphia, in collaboration with the Department of Pediatrics of the University of Pennsylvania and the Staff of the Camden Municipal Hospital. Tuition—$110.00.

2. Practical Pediatric Hematology. June 3, 4, and 5. Conducted by Irving J. Wolman, M.D., and other members of the Hematology Department of the Children's Hospital, under the auspices of the Graduate School of Medicine, University of Pennsylvania. Tuition—$75.00.

3. Blood Group Incompatibilities and Erythroblastosis Fetalis. June 6 and 7. Conducted by Neva Abelson, M.D., and Thomas R. Boggs Jr., M.D., of the Philadelphia Serum Exchange of the Children's Hospital of Philadelphia, under the auspices of the Graduate School of Medicine, University of Pennsylvania. Tuition—$50.00.

Inquiries should be addressed to Irving J. Wolman, M.D., Children's Hospital of Philadelphia, 1740 Bainbridge Street, Philadelphia 46, Pa.

Ninth Annual Summer Clinics of the Children's Hospital in Denver.—The Ninth Annual Summer Clinics of The Children's Hospital in Denver will be held June 24, 25, and 26, 1957. Designed for all physicians concerned with the care of children, the course will present recent advances in medical knowledge appropriate to the first few weeks of life, and will emphasize methods for the early recognition of disease, discuss emergency procedures of value, and outline successful programs of therapy.

Guest faculty this year will be Dr. Stewart H. Clifford, Assistant Clinical Professor of Pediatrics, Harvard Medical School, Dr. H. William Clatworthy Jr., Associate Professor of Pediatric Surgery, Ohio State University, and Dr. Edith L. Potter, Professor of Pathology, Department of Obstetrics and Gynecology, the University of Chicago.

Further information can be secured by writing the Chairman, Summer Clinics Committee, Children's Hospital, Denver 18, Colo.

Pediatric Education Award.—The preparation of others for a career of useful work provides a unique satisfaction that is rewarding in itself. While the effects of good teaching are readily appreciated, too frequently the teacher remains without acknowledgment of his efforts. The Ross Laboratories Award in Pediatric Education is established to encourage the development of new and more effective ways of teaching pediatrics and to show a small measure of gratitude for effectiveness in pediatric instruction.

Every two years the Western Society for Pediatric Research may confer this award on the nominee adjudged to have made the most significant contribution to the teaching of Pediatrics within the preceding *three* years. Ross Laboratories will donate $1000 and a suitably engraved plaque to be presented to the nominee at the annual meeting of the Society.

Nominations for the award will be accepted from any interested source, and should be submitted in quadruplicate, accompanied by written or documentary evidence permitting evaluation of the work submitted. No limitations are stipulated. The work may have been accomplished in any institution of undergraduate or postgraduate medical teaching within the geographic area represented by the Society.

The nominee's accomplishments shall be judged on the basis of demonstrated effectiveness and ability in enhancing the teaching of pediatrics. Any aspect of this broad field may be selected as exemplary.

The Education Award Committee requests nominations covering work accomplished since January of the *third preceding year*. Nominations will have closed April 30, so that the committee will have sufficient time to come to a decision prior to the annual meeting in October. The decision of the committee will be approved by the Executive Council of the Society before announcement of the award. The Committee may elect to divide the award among collaborators or between persons responsible for different accomplishments, if their judgement so desires.

Please mail directly to Robert H. Alway, M.D., Western Society for Pediatric Research, 2351 Clay St., San Francisco, Calif.

Summer Camp for Diabetic Children.—The Summer Camp for Diabetic Children will be opened for the eighth season under the auspices of the Chicago Diabetes Association, Inc., from July 14 to Aug. 4, 1957, at Holiday Home, Lake Geneva, Wis.

In addition to the complete camp personnel, the Chicago Diabetes Association furnishes a staff of resident physicians and dietitions, trained in the care of diabetic children.

Boys and girls, aged 8 through 14 years, are eligible. For further information regarding fees, interested persons should be directed to write or phone the office of the Chicago Diabetes Association. Fees will be set on a sliding scale to meet individual circumstances.

Physicians are urged to notify parents of diabetic children and to enter the names of children who would like to attend camp. Applications may be obtained from, and inquiries should be addressed to, the Chicago Diabetes Association, 5 S. Wabash Ave., Chicago 3, Ill., ANdover 3-1861.

Limited capacity necessitates prompt application.

Books

BOOK REVIEWS

Handbook of Poisons. By Robert H. Dreisbach. Price, $3. Pp. 426, with numerous illustrations. Lange Medical Publications, Box 1215, Los Altos, Calif., 1955.

This is the most complete handbook on the subject of poisons that this reviewer has seen. An amazing amount of up-to-date information is packed into this conveniently small book. Such recent agents as the antihistamines, chlorpromazine, and the new organic pesticides are well described and their hazards outlined. A large section discusses the hazards of poisonous plants, reptiles, and insects and the treatment of their effects. This is an indispensable source of reference.

On the Early Development of Mind. By Edward Glover. Price, $7.50. Pp. 483. International Universities Press, 227 W. 13 St., New York 11, July, 1956.

This book represents the first volume of a collection of papers published by the author over a period of 30 years. The author is a British psychoanalyst noted for his research and teaching in psychoanalysis.

The papers deal with some of the fundamental theoretical principles of psychoanalysis, particularly as applied to the early development of the mind.

The book will be of great value to the student of psychoanalysis but seems much too theoretical and involved to be of practical value to the pediatrician.

Preventive Medicine and Public Health—Eighth Edition. Edited by Kenneth F. Maxcy. Price, not given. Pp. 1462, with numerous illustrations. Appleton-Century-Crofts, Inc., 35 W. 32nd St., New York 1, 1956.

With the appropriate substitution of Public Health for Hygiene in the title and the inclusion of the more important new concepts, knowledge, and statistical data which have appeared during the last five years, Dr. Maxcy and his 26 collaborating authorities have completed their revision of Rosenau's textbook of preventive medicine. Of particular interest and value to pediatricians are the sections on the prevention of communicable diseases, nutrition and deficiency diseases, and maternal and child health which together make up approximately 50% of the 1462 page illustrated text. The sections on sanitation, environmental medicine, industrial medicine, public health administration, epidemiology, and statistics like the rest of the text are authoritative up to date summations of existing knowledge, thinking, and planning.

It can safely be predicted that this new edition will continue to maintain this book in the outstanding place it has held as the standard textbook and reference book in the field since its first edition in 1913.

The Year Book of Pediatrics (1956-57 Year Book Series). Edited by Sydney S. Gellis. Price, $6.75. Pp. 480, with 134 illustrations. Year Book Publishers, Inc., 200 E. Illinois St., Chicago 11, 1956.

Dr. Gellis has again done a superb job in the presentation of the current Year Book of Pediatrics. The material is presented in the same manner as in previous years, i. e., brief abstracts of articles pertinent to pediatrics from a great variety of journals are included and these are followed in many instances by appropriate editorial comments, either by the editor or by a recognized authority in the particular field under discussion. The articles abstracted are from journals received during the period from June, 1955, through May, 1956. The book is divided into sections as regards subject matter and the articles are grouped accordingly; examples of these divisions are The Premature and the Newborn, Nutrition and Metabolism, Infectious Disease and Immunity, etc.

The Year Book is a valuable contribution to pediatric literature in many ways. For those people who are unable to keep abreast of current literature this volume affords an opportunity for review, and, although one has read the original article, this book offers an

excellent chance to reappraise it particularly in light of the excellent editorial comments included. Finally, having the volume available affords a source of quick reference material which is relatively recent on most subjects which arise in pediatric practice. One is occasionally disappointed that a particular article is followed by no comment, but, on the other hand, one also occasionally gets the impression that the very omission of comment speaks rather eloquently in itself.

Masked Epilepsy. By Hugh R. E. Wallis. Price, $2.50. Pp. 51. Williams & Wilkins Company, Mount Royal and Guilford Aves., Baltimore 2, 1956.

This is an interesting monograph dealing primarily with the association of "cyclical vomiting" and "epilepsy." Dr. Wallis was one of the first to write on this subject and now presents information on 20 of his patients. The case histories reveal, in addition to cyclical vomiting, the chief complaints to have been periodic headaches, behavior disturbances, abdominal pain, and fever. The diagnosis is suggested by the character and paroxysmal nature of the complaints and by the association of a family history of epilepsy. It is confirmed by the finding of an abnormal electroencephalogram, although the author states that 20%-30% may have normal readings. The satisfactory response to anticonvulsant therapy is further evidence for this diagnosis.

The actual significance of this syndrome is open to some question, but there is growing evidence, such as this contribution, that the association is a real one. This monograph is not based on scientifically controlled study; consequently one has to bear in mind the danger of *post hoc* diagnosis. However, it does add to our knowledge in this field and is enjoyable reading.

Laboratory Tests in Common Use. By Solomon Garb. Price, $2. Pp. 160. Springer Publishing Co., 44 E. 23rd St., New York 10, April, 1956.

This is a small, simply written text aimed primarily at explaining the purpose and techniques of the common laboratory tests to nurses and office assistants. It should be satisfactory for this limited purpose, but it is disappointing to find very little caution regarding the interpretation of these tests. For example, in the section on hemoglobin determinations there is no statement regarding either the technical error inherent in the test or the variability at different ages. Since the erroneous diagnosis of anemia is repeatedly made by paramedical personnel, this should be stressed. This failure to note the difference between infants and adults recurs throughout the book.

Talking with Patients. By Brian Bird. Price, $3. Pp. 154. J. B. Lippincott Company, 227 S. Sixth St., Philadelphia 5, 1955.

Dr. Bird has written this small monograph to emphasize the importance of how a physician talks with his patients during history taking and also in connection with the management of illness, the approach of death, and even in the matter of fees. Approximately half of the volume is devoted to how to talk with children. Although most physicians learn how to do this as a matter of experience, there are many "pearls of wisdom" here for experienced pediatricians. This is interesting and enjoyable reading that can be recommended highly.

Bone Structure and Metabolism. Edited by G. E. W. Wolstenholme and Cecilia M. O'Connor the Ciba Foundation. Price, $8. Pp. 299, with 121 illustrations. Little, Brown & Company, 34 Beacon St., Boston, 1956.

This book contains a series of presentations and discussions of the presentations dealing with the newer concepts of the structure of bone. The structure of bone is developed in logical sequence starting with the anatomical approach, proceeding through the dynamic metabolism of the organic and inorganic constituents of bone, and linking the two approaches into a unified concept. Some of the material represents previously unpublished work and other material is summation of previously reported research.

The practicing physician may find that this book is difficult to read because of the many new and unfamiliar techniques employed in the elucidation of the structure of bone. A knowledge of autoradiographs, organic chemistry, and of isotope technique

is necessary for critical analysis of most of the individual papers. The almost complete lack of practical applications makes this book of little value in the clinical practice of medicine. The pediatrician and internist would find certain sections of interest. The discussion of variations in sensitivity to vitamin D is stimulating. The paper on the present knowledge of parathyroid function reviews newer concepts of the physiologic changes in parathyroid disease. The paper on osteodysmetamorphosis fetalis (hypophosphatasia) presents a relatively new syndrome from various points of view.

Knowledge of the metabolism of bone is advancing so rapidly that all physicians interested in physical growth or in bone disease should become acquainted with advances in this field. For physicians who are interested in more than immediately applicable information, this book will enable them to understand the increasing literature on the mechanism of bone disease and thus the physiologic approach to treatment of diseases involving bone.

A. M. A. Scientific Exhibits 1956. By the American Medical Association. Price, $10. Pp. 411. Grune & Stratton, Inc., 381 Fourth Ave., New York 16, December, 1956.

This book marks an innovation regarding the scientific exhibits shown at the annual meeting of the American Medical Association. In order to make the outstanding exhibits available to a larger number of viewers, a selected group has been compiled for publication. There are of special interest to pediatricians "Hormone Patterns in Rheumatic Fever," by Kelley, Ely, and Done, and "Diagnosis and Treatment of Moniliasis," by Dobias and Mitchell. It is probable that this collection of exhibits will be of more interest to general practitioners than to pediatricians.

J. A. M. A. Clinical Abstracts of Diagnosis and Treatment 1956. By the American Medical Association. Price, $5.50. Pp. 661. Grune & Stratton, Inc., 381 Fourth Ave., New York 16, June 15, 1956.

This collection of abstracts from *The Journal of the American Medical Association* will be of particular interest to general practitioners for reviewing recent literature in "capsule form." Although the use of abstracts leaves much to be desired, it does allow a busy practitioner to scan the literature in order to identify articles which require more careful review. Since the coverage is a broad one, there has been no attempt to list articles of particularly pediatric interest.

BOOKS RECEIVED

Diagnostico y Semiologia Pediatricos—Tomo II. By Calixto Torres Umana. Price, not given. Pp. 1350, with 185 illustrations. Editorial Omnia, Bogota, Colombia, 1956.

Children's Eye Problems. By Emanuel Krimsky. Price, $6. Pp. 175, with 35 illustrations. Grune & Stratton, Inc., 381 Fourth Ave., New York 16, December, 1956.

Die Pathogenese des Morbus haemolyticus neonatorum. By Gerhard Martius. Price, $2.30. Pp. 70. Intercontinental Medical Book Corporation, 381 Fourth Ave., New York 16, 1956.

Paper Electrophoresis. Prepared by the Ciba Foundation. Edited by G. E. W. Wolstenholme and Elaine C. P. Millar. Price, $6.75. Pp. 224, with 74 illustrations. Little, Brown & Company, 34 Beacon St., Boston 6, 1956.

Bone Structure and Metabolism. Prepared by the Ciba Foundation. Edited by G. E. W. Wolstenholme and Cecilia M. O'Connor. Price, $8. Pp. 299, with 121 illustrations. Little, Brown & Company, 34 Beacon St., Boston 6, 1956.

Services for Children with Hearing Impairment. Prepared by the American Public Health Association Committee on Child Health. Price, $1.50. Pp. 124. American Public Health Association, 1790 Broadway, New York 19, 1956.

Services for Children with Vision and Eye Problems. Prepared by the American Public Health Association Committee on Child Health. Price, $1.50. Pp. 112. American Public Health Association, 1790 Broadway, New York 19, 1956.

The Psychoanalytic Study of the Child—Volume XI. By Ruth S. Eissler et al. Price, $8.50. Pp. 470. International Universities Press, 227 W. 13 St., New York 11, December, 1956.

Pediatric Cardiology. By Alexander S. Nadas. Price, $12. Pp. 587, with 343 illustrations. W. B. Saunders Company, 218 W. Washington Square, Philadelphia 5, January, 1957.

The Physician-Writer's Book. By Richard M. Hewitt. Price, $9. Pp. 415, with 37 illustrations. W. B. Saunders Company, 218 W. Washington Square, Philadelphia 5, January, 1957.

Pica. By Marcia Cooper. Price, $3.75. Pp. 114. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., January, 1957.

Radiology of the Alimentary Tract in Infancy. By Roy Astley. Price, not given. Pp. 287, with numerous illustrations. Williams & Wilkins Company, Mount Royal and Guilford Aves., Baltimore 2, 1956.

Discussions on Child Development—2 Volumes. Edited by J. M. Tanner and Barbel Inhelder. Price, $10. Pp. Vol. 1, 240, with 21 illustrations; Vol. 2, 271, with 23 illustrations. International Universities Press, Inc., 227 W. 13 St., New York 11, February, 1957.

Oto-Rhino-Laryngologie Infantile. By A. Lemariey. Price, 6,200 francs. Pp. 826, with 300 illustrations. Masson & Cie, 120, boulevard Saint-Germain, Paris^{6e}, 1956.

Le Traitement de la Tuberculose de l'Enfant. Edited by R. Cruickshank.—President of the Seminaire, Dec. 1955. Price, 2,500 francs. Pp. 354, with 80 illustrations. Masson et Cie, 120, boulevard Saint-Germain, Paris^{6e}, 1956.

Congenital Anomalies of the Viscera. By J. L. Bremer. Price, $5. Pp. 202, with 89 illustrations. Harvard University Press, Cambridge 38, Mass., 1957.

Liver: Structure and Function. By Hans Popper and Fenton Schaffner. Price, $20. Pp. 777, with 204 illustrations. Blakiston Company (Division of McGraw-Hill Book Company, Inc.), 330 W. 42d. St., New York 36, 1957.

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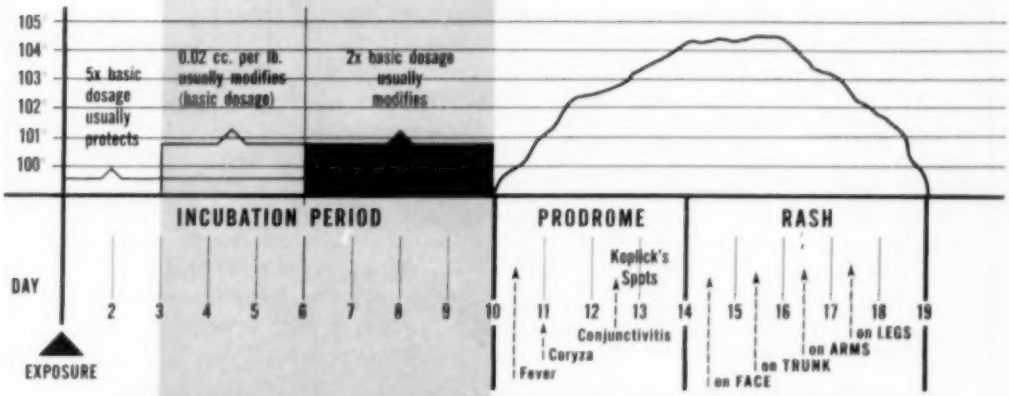

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1. Bowes, A. deP.: Dietotherapy—Nutrition of Children During Their School Years, Am. J. Clin. Nutrition *3*:254 (May-June) 1955.

2. Sebrell, W. H., Jr.: Trends and Needs in Nutrition, J.A.M.A. *152*:42 (May 2) 1953.

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1. Facts on Oats: Report by the Research Laboratories of The Quaker Oats Company, 1955.

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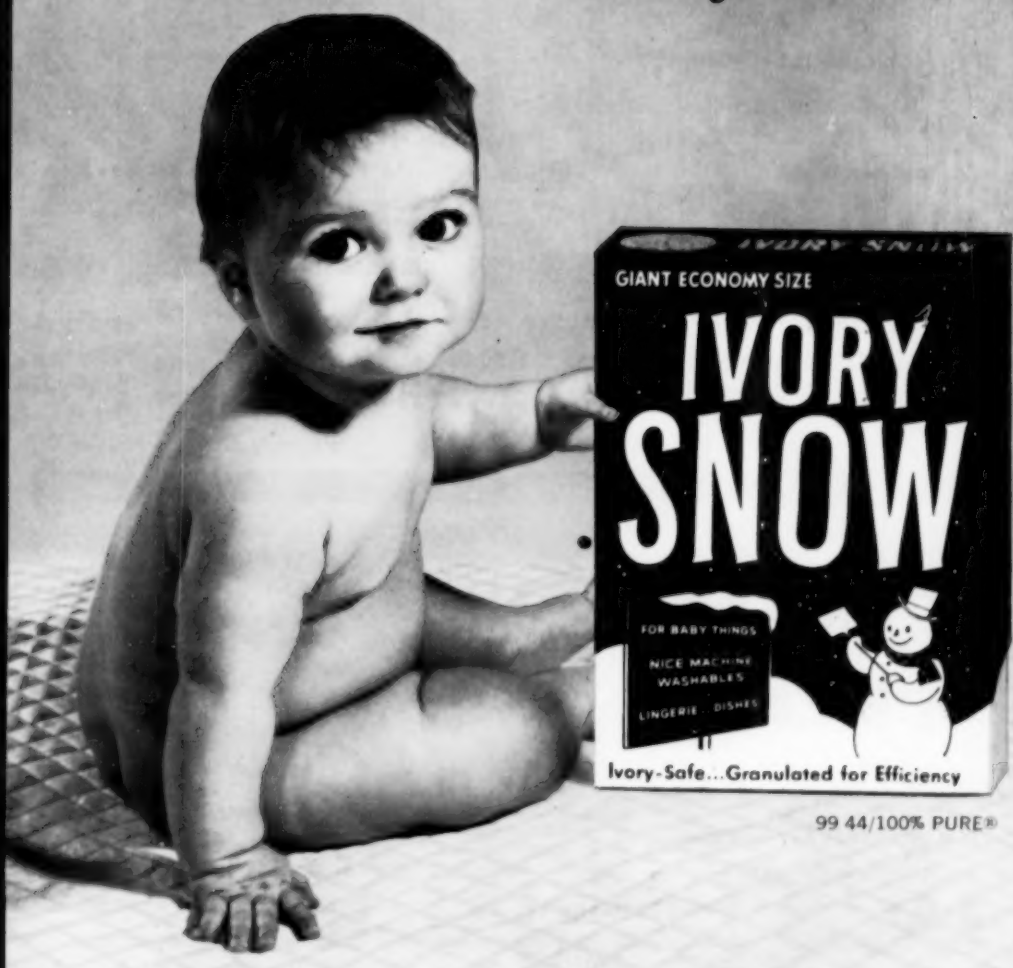

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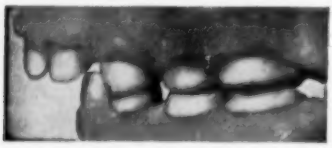

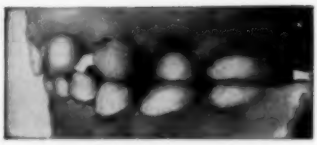

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